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A Symposium: Adjunctive Therapies in Thrombolysis

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GUEST EDITOR:

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Baylor College of Medicine
Chief of Cardiology
The Methodist Hospital
Houston, Texas

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JANUARY 25, 1991 VOL. 67 NO. 3

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Adjunctive Therapies in Thrombolysis

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The American Journal of Cardiology®

JANUARY 25, 1991 VOL. 67 NO. 3

A SYMPOSIUM: ADJUNCTIVE THERAPIES IN THROMBOLYSIS

1A
Introduction
Robert Roberts

3A
Heparin as an Adjunctive Treatment After Thrombolytic Therapy for Acute Myocardial Infarction
Martin H. Prins and Jack Hirsh

12A
Role of New Antiplatelet Agents as Adjunctive Therapies in Thrombolysis
James T. Willerson, Paolo Golino, Janice McNatt, John Eidt, Sheng-Kun Yao and L. Maximilian Buja

19A
Role of New Anticoagulants as Adjunctive Therapy During Thrombolysis
Paul R. Eisenberg

25A
Adjunctive Use of Beta-Adrenergic Blockers, Calcium Antagonists and Other Therapies in Coronary Thrombolysis
Richard C. Becker and Joel M. Gore

32A
Summary
Robert Roberts

The
American
Journal
of
Cardiology

Introduction

Robert Roberts, MD

The benefit of intravenous thrombolytic therapy in acute myocardial infarction (MI) has been firmly established by national and international clinical trials. Thrombolysis induced within the early hours of the onset of infarction is associated with limitations of infarct size, improved ventricular function, and a low hospital morbidity. However, soon after the initial trials, it became clear that lysis induced by thrombolytic therapy was followed by a significant incidence of reinfarction (10%), just as was observed with the putative spontaneous lysis that occurs with non-Q-wave infarction. The need for adjunctive therapy was appreciated and a significant reduction in reinfarction was observed with aspirin.

Recent studies suggest that heparin may reduce the reocclusion rate after thrombolysis in patients receiving recombinant tissue-type plasminogen activator (rt-PA). Ongoing research has also identified potential adjunctive strategies for future study that may shorten the time to thrombolysis and prevent reocclusion. Among these agents are thrombin, platelet and small peptide inhibitors, factor VIIa complex, monoclonal antibodies to platelet glycoprotein IIb/IIIa, and activated protein C. In addition, some studies have suggested that β blockers, calcium antagonists, angiotensin-converting enzyme inhibitors, and nitrates also may be useful adjuncts to thrombolytic therapy.

When thrombolytic therapy was first introduced, it was administered through the intracoronary route, and it became standard practice to administer heparin, probably to avoid catheter-related problems. It then became evident that intravenous administration was an effective alternative that would also minimize complications. In the absence of data from a prospective clinical trial, physicians continue to administer heparin with the conviction that it prevents reocclusion and, based on clinical data and rational empiricism, aspirin was added in the hope of preventing platelet aggregation and rethrombosis. The results of the Second International Study of Infarct Survival (ISIS-2) indicated improved survival in patients who received aspirin in conjunction with a thrombolytic agent. The results of several trials showing significant benefit in patients with ischemic cardiac disease, including unstable angina, further solidified the recommendation that aspirin be a part of routine postthrombolytic therapy. The most recent study by Theroux et al of patients with unstable angina shows marked reduction in the incidence of reinfarction with aspirin and a similar benefit with heparin and is relevant because a significant proportion of patients with unstable angina exhibit coronary thrombi. In the recent American College of Cardiology/American Heart Association (ACC/AHA) guidelines on the early management of patients with acute MI, it is recommended that aspirin be administered (160 mg immediately and continued on a daily basis indefinitely) in patients receiving thrombolytic therapy.

The role of heparin as an adjunctive treatment during and after thrombolytic therapy for acute MI remains highly controversial. Interest in this topic intensified after the publication of the Second Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico study, which reported that the addition of heparin to

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thrombolytic agents (streptokinase and t-PA) did not induce a further reduction in mortality. These findings prompted the statement, in a recent review by Yusuf et al, that "at present, adjunctive heparin therapy is not indicated in patients with acute MI who have been treated with thrombolytic therapy." In contrast, the recently published ACC/AHA guidelines strongly recommend the use of heparin in combination with or immediately after thrombolytic therapy.

The paucity of data regarding the comparative efficacy of adjunctive heparin versus adjunctive aspirin led to the Heparin-Aspirin Reperfusion Trial (HART). HART, a multicenter study involving 3 university hospitals, compared heparin with aspirin in 205 patients with acute MI who received t-PA. At 18 hours, 82% patency was observed in the heparin-treated patients, compared to 52% in the group that received t-PA plus aspirin, a difference that was statistically significant. These data suggested that the high early patency rates associated with t-PA can be sustained only with early concomitant systemic heparinization and not with aspirin as adjunctive therapy. These data are supported by a pilot study (Bleich et al) in which patients were randomized to t-PA plus heparin or t-PA alone. As in HART, sustained patency rates were significantly higher in the patients treated with a combined regimen of t-PA plus heparin. Recent evidence from the European Cooperative Study Group Trial (ECSG-6) also confirms the value of intravenous heparin as an adjunct to thrombolytic therapy with t-PA.

These studies, in conjunction with the Australian National Heart Foundation Study, confirm the necessity of heparin as adjunctive therapy when using t-PA in patients with acute MI. In addition, the results suggest that heparin is only necessary for the initial 24 to 48 hours, after which aspirin alone appears adequate. Aspirin inhibits platelet aggregation by inhibiting the synthesis of thromboxane and thus its beneficial results are expected. In contrast, the beneficial effect of heparin is more difficult to understand because heparin has no effect on platelets per se. Because the studies suggest that heparin is more effective during the first 24 to 48 hours after initiation of thrombolytic therapy, when thrombin levels are increased, it is reasonable to postulate that heparin exerts its antiplatelet action by neutralizing thrombin, a substance known to induce platelet aggregation. The ACC/AHA guidelines strongly recommend the use of heparin in combination with or immediately after thrombolytic therapy.

The role of β blockers and calcium antagonists as adjunctive agents remains to be resolved. These agents are often used during acute MI in the absence of reperfusion therapy, but little data are available as to whether either or both of these agents are beneficial after thrombolytic therapy. The results of the Second Thrombolysis in Myocardial Infarction (TIMI-2) study suggested that β blockers may be beneficial in preventing myocardial ischemia after thrombolysis. In ISIS-2 there was a suggestion that β blockers may prevent myocardial rupture; however, this was not confirmed in the TIMI-2 study. The ACC/AHA guidelines note that use of a calcium antagonist may be preferable to a β blocker after reperfusion because of the enhanced vasomotor activity produced by recanalization.

The papers included in this supplement entitled "Adjunctive Therapies in Thrombolysis" will further explore the role of heparin, aspirin, β blockers, calcium antagonists, and other new investigative approaches for antiplatelet and anticoagulant activity.

Heparin as an Adjunctive Treatment After Thrombolytic Therapy for Acute Myocardial Infarction

Martin H. Prins, MD, and Jack Hirsh, MD

The rationale for considering heparin therapy as an adjunct to thrombolytic treatment for patients with acute myocardial infarction is to prevent rethrombosis after successful thrombolysis. The risk of reocclusion is high immediately after thrombolysis because blood flowing through the newly opened coronary artery is exposed to thrombin bound to fibrin in the residual thrombus.

Clinical studies of patients with venous thrombosis and acute myocardial infarction indicate that there is a relation between the anticoagulant response to heparin and clinical efficacy and that the concept of a therapeutic heparin level is valid. Subcutaneous doses of approximately 15,000 U twice a day fail to provide an adequate anticoagulant response at 24 hours in the majority of patients, whereas intravenous administration of a bolus of 5,000 U followed by continuous infusion of 30,000 U per 24 hours produces an adequate anticoagulant response at 24 hours in approximately 80% of patients.

Studies of patients with myocardial infarction who received streptokinase showed a significant beneficial effect on mortality when 12,500 U of heparin was administered subcutaneously 2 times per day. In contrast, the single largest study evaluating heparin 12,500 U administered subcutaneously 2 times per day as an adjunct to recombinant tissue-type plasminogen activator (rt-PA) treatment did not show a beneficial effect on mortality. However, studies using full-dose intravenous heparin therapy demonstrated that heparin improves patency after coronary thrombolysis with rt-PA.

A plausible explanation for these apparently contradictory findings is that the need for heparin administered early in high doses is greater in patients treated with rt-PA than in those treated with streptokinase, because of the lesser systemic anticoagulant effects induced by rt-PA treatment.

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It is a fundamental tenet of biostatistical lore that failure to demonstrate benefit from a therapeutic intervention which is in truth effective could result from (1) an inadequate sample size; (2) the choice of an imprecise outcome measure (which increases the sample size requirement); and (3) bias. Another equally important reason for a false-negative result is the suboptimal use of the experimental intervention. The core of the controversy surrounding the value or lack of value of heparin therapy as an adjunct to thrombolytic therapy in acute myocardial infarction is based on the contention that heparin may have been used suboptimally in the 1 large reported trial addressing this topic and that it is being used suboptimally in the second trial, which is reaching completion.

The role of heparin as adjunctive treatment during and after thrombolytic therapy of acute myocardial infarction is highly controversial. Interest in this topic intensified after the publication of the Second Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI-2) study, which reported that the addition of heparin to thrombolytic agents (streptokinase and recombinant tissue-type plasminogen activator [rt-PA]) does not contribute to mortality reduction, although it does increase the incidence of bleeding.[1,2] These findings prompted the statement in a recent review that "at present, adjunctive heparin therapy is not indicated in patients with acute myocardial infarction who have been treated with thrombolytic therapy."[3] In contrast, the recently published guidelines of the American College of Cardiology and American Heart Association on the early management of patients with acute myocardial infarction took an opposite view and strongly recommended the use of heparin in combination with or immediately after thrombolytic therapy.[4]

The issues relating to the role of heparin in coronary thrombolysis are complex. The question of the need or lack of need for heparin cannot be separated from the fundamental questions of the dosage of heparin, the intensity of anticoagulant effect, and the timing and route of heparin administration. It has been argued that the timing, dosage and route of heparin administration in the GISSI-2/International trials were suboptimal and that these shortcomings may not be resolved by the Third International Study of Infarct Survival (ISIS-3). Furthermore, it could be argued that the failure to use an optimal heparin regimen may have disadvantaged patients randomized to receive rt-PA more than those randomized to receive streptokinase, because rt-PA produces less of a systemic anticoagulant effect than streptokinase.[5]

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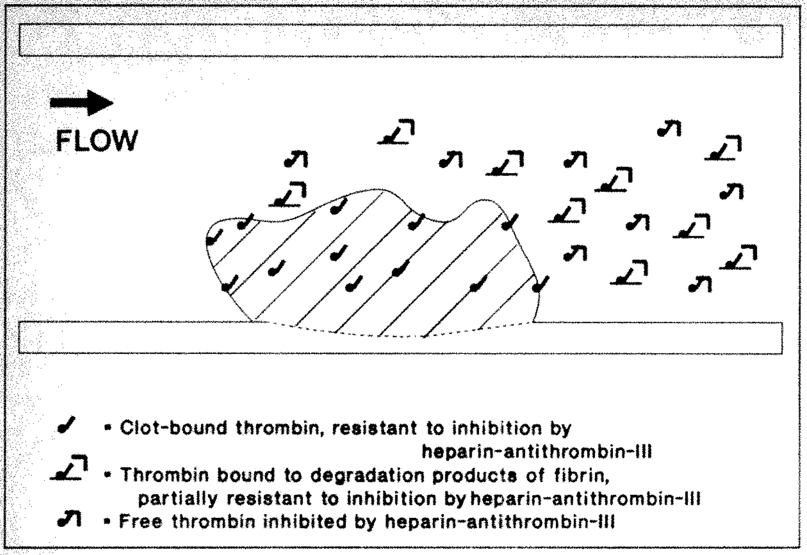
FLOW
• Clot-bound thrombin, resistant to inhibition by heparin-antithrombin-III
• Thrombin bound to degradation products of fibrin, partially resistant to inhibition by heparin-antithrombin-III
• Free thrombin inhibited by heparin-antithrombin-III

FIGURE 1. A thrombus, located on an atherosclerotic lesion, contains adsorbed thrombin. Fibrin-bound thrombin is resistant to inactivation by heparin. Thrombin bound to fibrin-fragments that are released during thrombolysis is less resistant to heparin inactivation, whereas thrombin produced through the autocatalytic effect of fibrin-bound thrombin is readily inactivated by the heparin-antithrombin-III complex.

In this report, we not only will review the results of studies that evaluated heparin as an adjunct to thrombolytic therapy in acute myocardial infarction, but also will consider the following fundamental issues: (1) the theoretical basis for adjunctive heparin treatment in coronary thrombolysis; (2) the pharmacokinetics of heparin and their influence on the dose response of heparin administered by intravenous and subcutaneous injection; and (3) the concept of a therapeutic range for heparin and evidence for its validity. Finally, an attempt will be made to interpret the results of the previously reported studies on heparin use in trials of thrombolytic therapy conducted in patients with acute myocardial infarction in light of these fundamental observations.

BIOLOGIC RATIONALE FOR USE OF HEPARIN AFTER THROMBOLYSIS

The beneficial effects of rapid coronary thrombolysis on myocardial function can be abrogated by early reocclusion, which, if prevented, would be expected to improve patient survival. The results of recent laboratory studies indicate that the process of coronary thrombolysis produces conditions in the newly opened coronary artery that can favor early rethrombosis.[6–8] Thus, blood perfusing the reopened artery is exposed to high concentrations of thrombin, which is adsorbed onto the fibrin surface of both the lysing thrombus and the resulting soluble fibrin degradation products. The fibrin-bound thrombin can lead to reocclusion by interacting directly with plasma fibrinogen or by stimulating the production of more thrombin by activating an autocatalytic process. Thrombin bound to fibrin is much more resistant than free thrombin to inhibition by heparin/antithrombin III complex (Figure 1).[9,10] Nevertheless, a recent study that used an assay for fibrinopeptide A as a marker for unregulated thrombin activity showed that enhanced fibrinopeptide A production during coronary thrombolysis can be inhibited by the concomitant administration of an intravenous bolus of 5,000 U of heparin.[7,8] This finding suggests that heparin has the potential to prevent reocclusion by inactivating the free thrombin that is formed in the vicinity of the lysing thrombus.

HEPARIN PHARMACOKINETICS

Data from animal studies: Animal experiments indicate that heparin is cleared from the circulation by 2 different mechanisms: a saturable cellular and a nonsaturable renal clearance.[11] With low dosages of heparin, the saturable mechanism predominates, whereas with higher dosages the nonsaturable mechanism is more important.[11] This pattern of clearance explains the following 3 observations: (1) heparin plasma levels, after a large intravenous bolus, show a concave-convex pattern of clearance[12]; (2) the half-life of heparin increases progressively with increasing plasma levels of heparin[11]; and (3) the recovery in plasma of heparin activity (plasma recovery) in rabbits of subcutaneously administered unfractionated heparin compared to that of heparin administered by an intravenous bolus varies from <30% for a dose of 500 U/kg to >90% for dosages reaching as high as 5,000 U/kg.[13]

Data from human studies: After intravenous bolus injection of 250 anti-Xa U/kg heparin in healthy volunteers, the same concave-convex pattern of heparin disappearance is seen as in the animal studies.[14]

Comparative studies of the plasma recovery of heparin administered by intravenous and subcutaneous routes have been performed only with low dosages of heparin (≤7,500 U).[11,15,16] At these low dosages, the bioavailability of subcutaneous heparin is only 23 to 30%. The findings of a recent clinical trial demonstrated that the plasma recovery over the first 24 hours of high doses of subcutaneous heparin (15,000 U twice a day, after an intravenous bolus of 5,000 U) is considerably less than is seen with an identical dose given as a continuous intravenous infusion.[17] The plasma recovery of subcutaneous heparin improves when heparin treatment is continued for days, presumably because there is a gradual saturation of the cellular mechanism of heparin clearance. With high-dose intravenous heparin, saturation of the cellular clearance mechanism is much more rapid.

EVIDENCE FOR THE VALIDITY OF THE CONCEPT OF THERAPEUTIC HEPARIN LEVELS

Animal studies evaluating the effect of different heparin doses on the growth of an experimental venous thrombus showed that heparin levels of 0.2 to 0.4 U/ml measured by protamine titration are effective in preventing extension of the thrombus.[18] These levels are comparable to an activated partial thromboplastin time (APTT) ratio of approximately 1.5 to 2.5 (using a responsive thromboplastin), anti-Xa levels of 0.3 to 0.7 U/ml, or a whole blood clotting time that is prolonged two- to fourfold.[18]

Two studies of venous thromboembolism and 3 studies of myocardial infarction investigated the relation between results of coagulation tests after heparin administration and (recurrent) thrombotic events.

Hull et al[17] investigated the relation between the recurrence of venous thromboembolism in patients treated with either subcutaneous or intravenous heparin to the anticoagulant effect achieved. Recurrent venous thromboembolism occurred in 13 of the 53 patients who had an APTT <1.5 times control at 24 hours after initiation of heparin therapy and in only 1 of the 62 patients who had an adequate anticoagulant response at this time (relative risk 15.0).

In the study of Basu et al[19] patients with venous thromboembolism were treated with intravenous heparin and followed prospectively for evidence of recurrent thromboembolism. Among 67 patients who had an APTT <50 seconds for ≥ 2 consecutive days, 5 (7.5%) had a recurrence, compared to none of the 90 patients who had an adequate anticoagulant effect (relative risk 10.7).

Turpie et al[20] treated patients with acute anterior myocardial infarction with 12,500 U heparin subcutaneously 2 times per day and compared the heparin levels in the patients who developed a left ventricular mural thrombus to the levels of those who did not. The mean heparin levels were statistically significantly lower (0.10 ± 0.029 [$n = 10$] vs 0.19 ± 0.019 U/ml [$n = 85$], $p < 0.01$) in the patients who developed a left ventricular mural thrombus (estimated relative risk 22.2, assuming a normal distribution).

Kaplan et al[21] treated 75 consecutive patients with streptokinase followed by full-dose intravenous heparin treatment and related the incidence of myocardial ischemia to the anticoagulant effects achieved (measured with a partial thromboplastin time [PTT] assay). The investigators state that episodes of definite myocardial ischemia were 6 times more likely to be associated with PTT values <50 seconds than with PTT values >100 seconds.

Camilleri et al[22] performed a retrospective cohort analysis of 70 patients with myocardial infarction who were treated with 1.5 million U streptokinase followed by heparin infusion. Heparin therapy was monitored daily by APTT measurements. Recurrent ischemic events (signs of angina or infarction) occurred in 13 patients during periods when the APTT ratio was <1.5 (176 measurements) and in only 2 patients (359 measurements) when the APTT ratio was >1.5 (relative risk 13.3).

TABLE I Relative Risk of Thrombotic Outcomes in Anticoagulated Patients Using an Activated Partial Thromboplastin Time Ratio of 1.5 as a Cutoff in Cohort Analytic Studies

Study	Patient Type	Outcome	No.	RR
Hull et al[17]	DVT	Recurrent VTE	115	15.0
Basu et al[19]	DVT	Recurrent VTE	157	10.7
Turpie et al[20]	AMI	LVMT	112	22.2
Camilleri et al[22]	AMI	Recurrent MI/AP	70	13.3

AMI = acute myocardial infarction; AP = angina pectoris; DVT = deep vein thrombosis; LVMT = left ventricular mural thrombosis; RR = risk reduction; VTE = venous thromboembolism.

(The study of Kaplan et al[21] used partial thromboplastin time measurements rather than activated partial thromboplastin time values and the results are discussed in the text.)

These 5 independent observations from cohort analytic studies in 3 different clinical settings suggest that there is a relation between the absence of an adequate heparin response and the occurrence of thrombosis-related events during therapy with heparin and that the relative risk of thrombotic events when heparin therapy is inadequate is increased markedly, compared to the event rate with adequate heparin therapy (6.0 to 22.2) (Table I).

ANTICOAGULANT RESPONSE AFTER SUBCUTANEOUS OR INTRAVENOUS HEPARIN ADMINISTRATION

Healthy volunteers: In their study on the kinetics of intravenous heparin in healthy human subjects, de Swart et al[14] determined the clearance parameters for heparin and predicted that plateau levels of heparin of 0.2 to 0.4 U/ml would be reached only with doses $>25{,}000$ U per 24 hours (Figure 2). This prediction was confirmed by conducting a heparin infusion study in a limited number of volunteers.

Patients: In a prospective study it was found that when heparin is given intravenously as a continuous infusion starting at 30,700 U per 24 hours after an intravenous bolus of 5,000 U and the heparin dose is adjusted using a nomogram, an APTT >50 seconds (>1.5 times normal) is reached in 82% of patients at 24 hours and in 91% at 48 hours (Cruickshank MK et al, unpublished observations). The mean heparin dose required to produce an APTT above the lower level of the therapeutic range was 32,903 U per 24 hours.

In the study of Hull et al,[17] in which patients with venous thromboembolism received heparin either intravenously or subcutaneously, it was found that, after 24 hours, 29% ($n = 58$) of the patients who received intravenous heparin had subtherapeutic heparin levels versus 63% ($n = 57$) of the patients who were treated with subcutaneous heparin. This impressive and statistically significant difference in anticoagulant effect was reached

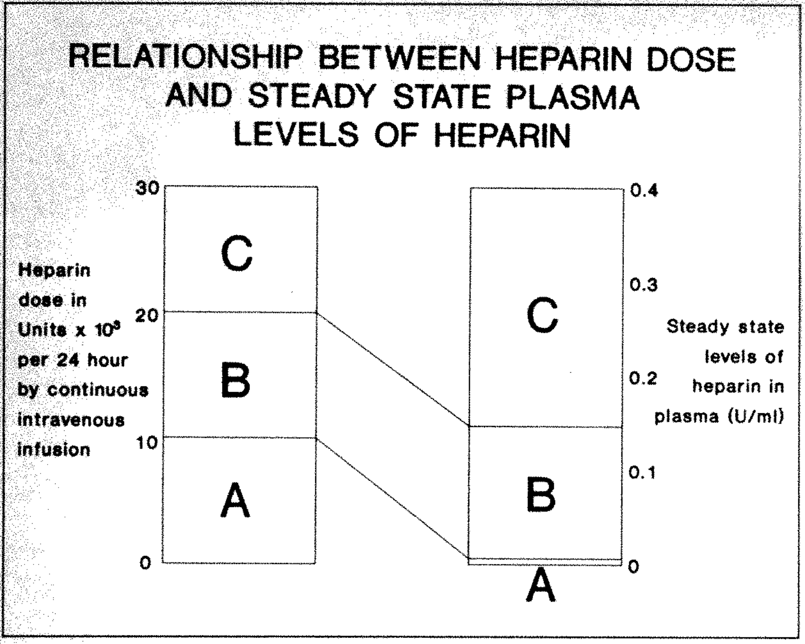
RELATIONSHIP BETWEEN HEPARIN DOSE AND STEADY STATE PLASMA LEVELS OF HEPARIN
Heparin dose in Units x 10³ per 24 hour by continuous intravenous infusion
30
20
10
0
C
B
A
0.4
0.3
0.2
0.1
0
C
B
A
Steady state levels of heparin in plasma (U/ml)

FIGURE 2. *A*, almost all of the heparin is rapidly cleared by the saturable cellular mechanism; plasma heparin levels are virtually undetectable. *B*, most heparin is cleared by the cellular mechanism, but a proportion of the heparin dose appears in the plasma and is cleared by a less rapid nonsaturable renal clearance mechanism. Plasma levels of heparin are measurable, but are below the lower limit of the therapeutic range. *C*, the cellular clearance mechanism is saturated. Most of the heparin is cleared by the nonsaturable clearance mechanism. Plasma heparin reaches therapeutic concentrations.[11,14]

despite a slightly higher heparin dose during the first 24 hours in the patients treated by subcutaneous injection (30,351 vs 28,484 U/24 hours).

One early study examined the time delay before achieving a therapeutic heparin level (measured by whole blood clotting time) using an initial dose of 20,000 U of heparin.[23] It was stated that in the majority of patients a therapeutic level was reached after approximately 1 to 2 hours and that this effect lasted for 10 hours after the injection; peak levels were reached 5 to 6 hours after injection.

Review of the results of a study reported by Turpie et al[20] of acute myocardial infarction, which used 12,500 U of heparin 2 times per day subcutaneously, is highly relevant to the interpretation of the results of the GISSI-2/International trials and ISIS-3 study.[1,2] The anticoagulant effects of heparin were measured daily, 6 hours after the subcutaneous injection. The mean heparin level on the first day of treatment was 0.11 U/ml and the APTT was barely prolonged over the control value. Mean APTT and heparin levels increased to just below the lower limit of the therapeutic range on the subsequent days of follow-up. This indicates that virtually all patients who received 12,500 U of heparin 2 times per day had subtherapeutic heparin levels during the first day of treatment and that approximately 50% had subtherapeutic peak levels during the remaining period of treatment.

In summary, when heparin is given as an intravenous bolus of 5,000 U and is followed by continuous infusion of approximately 30,000 U per 24 hours, therapeutic levels are achieved at 24 hours in the majority of patients, whereas subcutaneous administration of the same dose (15,000 U 2 times per day after an intravenous bolus of 5,000 U) does not achieve an adequate anticoagulant effect at 24 hours in the majority of patients. Doses of 12,500 U 2 times per day subcutaneously fail to provide adequate anticoagulation in approximately 50% of patients during the entire period of therapy. All of these observations on dose-response to heparin were made in patients not treated with thrombolytic agents, and it is possible that dosage requirements might be lower following thrombolytic therapy.

IMPACT ON EFFICACY PARAMETERS

Patency: The earliest randomized controlled trial examining the effect of heparin on patency is the Third Thrombolysis and Angioplasty in Myocardial Infarction trial,[24] in which 134 patients with acute myocardial infarction of recent (<6 hour) onset received rt-PA (6 mg/kg during 4 hours) with or without an intravenous bolus of 10,000 U of heparin. Coronary angiography was performed 90 minutes after initiation of therapy and showed a patency rate of 79% in both groups. This result excludes a true difference in patency rates at 90 minutes in favor of heparin of >14% with 95% confidence.

In the Heparin-Aspirin Reperfusion Trial (HART),[25] which was performed in 3 university hospitals, 205 patients with acute myocardial infarction of recent (<6 hours) onset were treated with 100 mg of rt-PA over 6 hours. Patients were randomized to either aspirin (80 mg/day) or to intravenous heparin (bolus of 5,000 U, followed by a continuous infusion of 1,000 U/hour titrated to an APTT ratio of 1.5 to 2 simultaneously with rt-PA). Patency measured by coronary angiography at a mean of 18 hours after infarction was 82% (n = 106) in the heparin group and 52% (n = 99) in the aspirin group. This difference is statistically significant at the $p < 0.0001$ level. In a trial by Bleich et al,[26] 83 patients with acute myocardial infarction of recent onset (<6 hours) were treated with 100 mg of rt-PA for 3 hours. Simultaneously with this regimen, patients were randomized to intravenous heparin (bolus of 5,000 U, followed by 1,000 U/

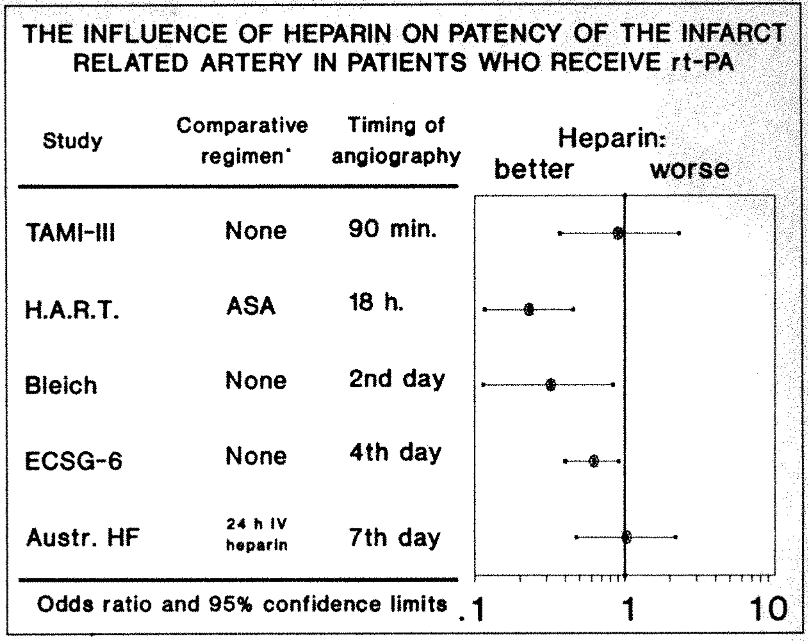

FIGURE 3. Influence of heparin on patency of the infarct-related artery in patients who receive recombinant tissue-type plasminogen activator. *Intravenous heparin was given simultaneously with rt-PA treatment in all of these studies. In the Third Thrombolysis and Angioplasty in Myocardial Infarction study, 10,000 U of heparin was given as a single bolus; in the other studies, 5,000 U of heparin was given as a bolus followed by 24,000 U/24 hours by continuous infusion[24–26] (Sixth European Cooperative Study Group Trial, National Heart Foundation of Australia, unpublished observations). ASA = acetylsalicylate; Austr. HF = Australian Heart Foundation; Bleich = reference 26; H.A.R.T. = Heparin-Asprin Reperfusion Trial; IV = intravenous.

hour, adjusted to an APTT 1.5 to 2 times normal) or no heparin. Coronary angiography was performed 2 days after the acute event to assess patency. Patency (Thrombolysis in Myocardial Infarction [TIMI] grade 2 to 3) was present in 30 of 42 patients (71%) in the heparin group and in 18 of 41 patients (44%) who did not receive heparin. This difference is statistically significant ($p < 0.023$, 2-tailed chi-square test with Yates correction).

In the recently completed Sixth European Cooperative Study Group (ECSG-6) trial, all patients received 100 mg of rt-PA and aspirin, either 250 mg intravenously or 300 mg orally, followed in both cases by 75 to 125 mg of aspirin on alternate days (unpublished observations, presented at the XII Congress of the European Society of Cardiology, 1990). Patients were randomized to heparin (intravenous bolus of 5,000 U followed by 1,000 U/hour titrated to 1.5 to 2 times control) or no heparin. Coronary angiography was performed at day 2 to 5 (mean 81 hours). Patency was present in 271 of 361 patients (83%) who received heparin therapy and in 244 of 326 patients (75%) who did not. This difference is statistically significant ($p < 0.01$, 2-tailed chi-square test) and consistent with the results of the 2 earlier trials.

The Australian National Heart Study addressed the question of the length of intravenous heparin therapy after 100 mg of rt-PA (National Heart Foundation of Australia Coronary Thrombolysis Group, unpublished observations). After thrombolytic treatment, all 202 patients received intravenous heparin for 24 hours. Thereafter, patients were randomized into groups that received either continuous intravenous heparin therapy or daily administration of 300 mg of aspirin and 300 mg of dipyridamole orally. Patency at 1 week was 80% in both groups ($n = 101$, $n = 94$, respectively). This excludes a true difference in patency rates at 1 week of >13% with 95% confidence, but the study does not have the power to exclude the 8% difference that was demonstrated in the much larger ECSG-6 study.

It would be inappropriate to pool the results of these 5 studies because the outcome of interest (patency) was measured at different periods of time after thrombolysis. Review of the results of the individual studies (Figure 3) suggests the following interpretation: Heparin does not improve patency at 90 minutes, at which time patency is largely dependent on the efficacy of the thrombolytic agent; heparin does, however, maintain patency during the first few days after coronary thrombolysis with rt-PA by preventing rethrombosis.

There have been no randomized trials published which assessed the effect of heparin therapy on patency in patients receiving anisoylated plasminogen streptokinase activator complex (APSAC), or (pro)urokinase.

Left ventricular mural thrombosis: STREPTOKINASE: The Studio sulla Calciparina nell'Angina e nella Thrombosi Ventriculare nell'Infarto (SCATI) trial reported on the prevalence of left ventricular mural thrombosis in patients with acute myocardial infarction who arrived at the hospital within 6 to 24 hours after onset of symptoms.[27] Those who presented within 6 hours of onset received streptokinase; those who presented after 6 hours of onset did not. All patients were randomized to receive heparin (an intravenous bolus of 2,000 U followed after 9 hours by 12,500 U every 12 hours) or no anticoagulant treatment. Left ventricular mural thrombus was assessed by echocardiography on the day of discharge in the patients with a first transmural acute anterior infarction. The prevalence of left ventricular mural thrombosis at discharge in patients who had a first acute transmural anterior myocardial infarction was 19 of 107 (17.7%) in the high-dose heparin group and 34 of 93 (36.6%) in the patients who did not receive anticoagulant therapy. This difference was statistically significant ($p < 0.01$). A sepa-

TABLE II Incidence of Reinfarction and Recurrent Ischemia in Randomized Clinical Trials Evaluating Heparin as Adjunctive Treatment After Coronary Thrombolysis

Outcome/ Study	Thrombolytic Agent/Incidence of Recurrent Event						p Value
	Heparin Regimen		Heparin		No Heparin		
			(n/n)	(%)	(n/n)	(%)	
Reinfarction							
SCATI[27]	SK	1[*]	18/218	8.2	21/215	9.7	0.70
GISSI-2[1,2]	SK	1	158/5,191	3.0	156/5,205	3.0	0.94
GISSI-2[1,2]	rt-PA	1	127/5,170	2.5	147/5,202	2.8	0.27
TAMI-3[24]	rt-PA	2	3/64	4.7	2/70	2.9	0.92
Bleich[26]	rt-PA	2	4/42	9.5	3/41	7.3	0.97
Aust. HF[†]	rt-PA	2	5/99	5.1	2/103	1.9	0.41
Recurrent ischemia							
SCATI[27]	SK	1	31/218	14.2	42/215	19.6	0.18
TAMI-3[24]	rt-PA	2	14/64	21.9	16/70	22.9	0.94
ECSG-6[†]	rt-PA	2	30/326	9.2	38/326	11.7	0.37

[*] = + 2,000 U intravenously immediately.
[†] = unpublished studies.
Aust. HF = Australian Heart Foundation; ECSG-6 = Sixth European Cooperative Study Group trial; GISSI = Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico; SK = streptokinase; TAMI = Thrombolysis and Angioplasty in Myocardial Infarction; rt-PA = recombinant tissue plasminogen activator; 1 = 2 times/day of 12,500 U heparin subcutaneously begun >9 hours after thrombolysis; 2 = immediate 5,000 U bolus intravenous heparin plus 24,000 U/24 hours adjusted to activated partial thromboplastin time 1.5 to 2 times control.

TABLE III Mortality Rates in Trials Evaluating Addition of Heparin to Thrombolytic Treatment

Lytic Agent/ Study	Incidence With				p Value
	Heparin SC 12,500 bid		No Heparin		
	(n/n)	(%)	(n/n)	(%)	
Streptokinase					
SCATI[27]	10/218	4.5	19/215	8.8	0.05
GISSI-2, all[1,2]	408/5,191	7.9	479/5,205	9.2	0.016
GISSI-2, after initiation of heparin[1,2]	254/5,037	5.0	311/5,037	6.2	0.015
rt-PA					
GISSI-2, all[1,2]	476/5,170	9.2	453/5,202	8.7	0.39
GISSI-2, after initiation of heparin[1,2]	294/4,988	5.9	298/5,047	5.9	0.98

SC = subcutaneously; other abbreviations as in Table II.

rate analysis for patients who did or did not receive streptokinase was not reported.

RECOMBINANT TISSUE-TYPE PLASMINOGEN ACTIVATOR: The ECSG-6 trial (design described earlier) also studied the prevalence of left ventricular mural thrombosis assessed by angiography at a mean time of 81 hours (ECSG-6, unpublished observations). The incidence was 3.7% in the heparin group and 6.8% in the nonheparin group (difference not significant).

Recurrent cardiac ischemia: Data are summarized in Table II. None of the studies that used the subcutaneous regimen and none of those that used the high-dose intravenous regimen demonstrated a statistically significant beneficial effect of heparin on reinfarction or recurrent cardiac ischemia.

Mortality: STREPTOKINASE: The earliest study to evaluate heparin as an adjunctive treatment to thrombolysis with streptokinase was the SCATI study (design described earlier).[27] The mortality rate was 4.5% (n = 218) among patients who received heparin and 8.8% (n = 215) among those who did not (p = 0.05). In the GISSI-2/International trials, the same trend was seen among patients who received streptokinase.[1,2] The design of this trial is shown in Figure 4. Among the patients who received streptokinase and heparin, the mortality rate was 7.9% (408 of 5,191), whereas it was 9.2% (479 of 5,205) in the group that received streptokinase alone; this difference is statistically significant (p <0.02). The analysis included patients who died before heparin treatment was commenced, and therefore before it could have influenced the outcome. When patients who died before heparin was started were excluded from the analysis, the same trend is still apparent: 5.0% (254 of 5,037) versus 6.2% (311 of 5,037) (p <0.02). These data indicate that 12,500 U of heparin administered subcutaneously 2 times per day beginning 9 to 12 hours after streptokinase, with or without an intravenous bolus of heparin after streptokinase, is a useful adjuvant to streptokinase treatment of patients with acute myocardial infarction of recent onset (Table III).

The results of these randomized studies are supported by data from the cohort analysis of the patients entered in the ISIS-2 trial.[28] In this study, patients were randomized to receive streptokinase or no thrombolytic treatment. Heparin treatment was not mandated by the study treatment protocol but used at the discretion of the attending physician and the intention to use heparin was recorded. The patients who received heparin (either subcutaneously or intravenously) in addition to streptokinase had a mortality rate of 8.7% (n = 5,655) whereas this rate was 10.1% (n = 2,937) among those who did not (p = 0.034). Because patients were not randomly allocated to receive heparin or no heparin, these results are subject to bias.

RECOMBINANT TISSUE-TYPE PLASMINOGEN ACTIVATOR: Currently, there is only 1 large randomized clinical trial (GISSI-2/International Trial) in which patients who received rt-PA treatment were randomized to receive 12,500 U of heparin subcutaneously after 12 hours, or no

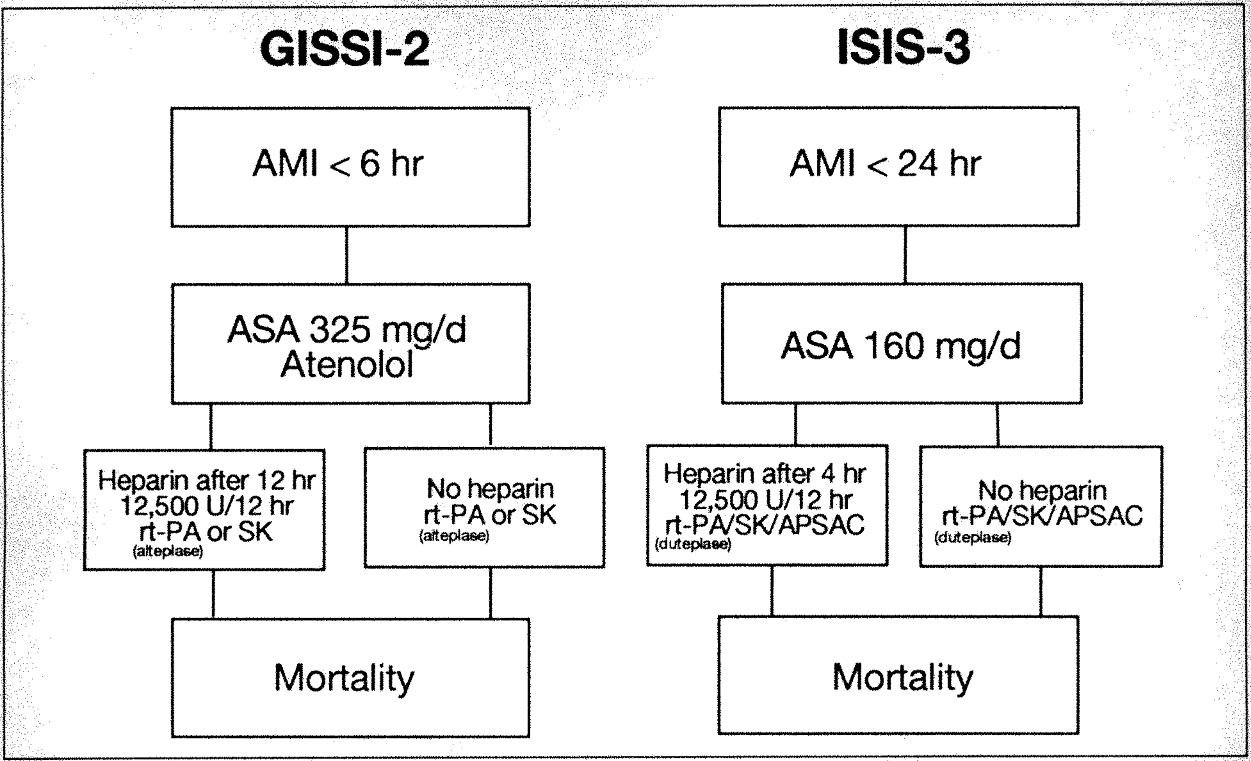

FIGURE 4. The patients in the Second Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico/International trials were randomly allocated to receive either streptokinase or tissue plasminogen activator treatment and those in the Third International Study of Infarct Survival trial to receive either streptokinase (SK), rt-PA or anisoylated plasminogen streptokinase activator complex (APSAC) treatment independently of the allocation to heparin treatment (factorial design). (*Note that the rt-PA used in this trial is duteplase, a double-chain form of rt-PA manufactured by Burroughs Wellcome Co. that is no longer under development.)

heparin (Figure 4). The mortality rate among the patients who received rt-PA and heparin was 9.2% (476 of 5,170); for those who received rt-PA not followed by heparin, it was 8.7% (453 of 5,202) ($p = 0.393$) (Table III). This negative trend in the heparin group was accounted for by deaths that occurred before the initiation of heparin therapy and therefore is only due to chance. After excluding the patients who died before heparin was started, the mortality rates are 5.9% (294 of 4,988) among those who received heparin and 5.9% (298 of 5,047) among those who did not ($p = 0.984$). This result excludes a true difference of greater than 1% with 95% confidence.

Other trials and agents: The recently begun ISIS-3 trial will randomize patients, using a factorial design, to streptokinase, APSAC or rt-PA (duteplase, Burroughs Wellcome formulation of double-chain rt-PA) and to 12,500 U of heparin 2 times per day subcutaneously, begun after 4 hours, or no heparin (Figure 4). The primary end point is vascular mortality during the first 5 weeks. Pending the results of ISIS-3, there are no reliable data available regarding the use of heparin in conjunction with APSAC; therefore, the need for heparin in APSAC-treated patients is unclear, as is the use of heparin with pro-urokinase (single-chain urokinase plasminogen activator).

Bleeding: The results of the GISSI-2/International trials clearly demonstrate that the addition of heparin therapy to thrombolytic treatment increases the risk of bleeding.[1,2] The reported incidence of minor bleeds was 594 of 6,195 (9.6%) among patients who received heparin and 328 of 6,206 (5.3%) among those who did not (risk reduction 1.88, $p < 0.001$, GISSI centers only). The incidence of major bleeds was 103 of 10,361 (1%) in the heparin group and 57 of 10,407 (0.5%) in the nonheparin group (risk reduction 1.79, $p < 0.01$, GISSI and International Trial centers).

Detailed information on the incidence of fatal bleeding or bleeding leading to permanent damage (e.g., intracranial hemorrhage) is required to assess the trade-off between the risks and benefits of heparin. In the GISSI-2 study, the incidence of hemorrhagic stroke was 0.3% ($n = 10,361$) among the patients who received heparin and 0.4% ($n = 10,407$) among those who did not. These figures suggest that the heparin regimen used in this study was not associated with an increased incidence of serious bleeding.

CONCLUSION

There is experimental evidence in humans that thrombolytic therapy is associated with activation of coagulation[6–8] and that this activation process can be modified by an intravenous bolus of 5,000 U of heparin.[7,8] There is also good evidence that the addition to rt-PA treatment of an intravenous bolus of heparin followed by a continuous infusion aimed at an APTT ratio of >1.5 improves the patency rate of the infarct-related coronary artery[25,26] (ECSG-6, unpublished observations). However, heparin in the dose of 12,500 U 2 times per day subcutaneously did not reduce the mortality rate in patients with acute myocardial infarction who were treated with rt-PA, but did reduce it in those who were treated with streptokinase.[1,2] This discrepancy forms the core of the controversy surrounding the use of heparin after thrombolytic therapy for acute myocardial infarction.

The results of studies analyzed in this review indicate that the clinical effectiveness of heparin is influenced strongly by its anticoagulant effect measured ex vivo and that the anticoagulant effect is influenced by the dose of heparin and its method of administration. In patients with venous thrombosis, failure to obtain an early therapeutic anticoagulant effect (APTT ratio 1.5 to 2.0, equivalent to a heparin level of 0.2 to 0.4 U/ml using protamine titration or 0.3 to 0.7 U/ml using an anti-Xa assay) results in a marked increase in the recurrence rate.[17,18] One of these studies in venous thrombosis also revealed that 15,000 U of heparin subcutaneously given 2 times per day produced a subtherapeutic anticoagulant response at 24 hours in the majority of patients.[17] The relation between the heparin regimen and clinical effectiveness in patients with acute myocardial infarction is less consistent. Subgroup analysis of patients with acute myocardial infarction indicates that there is a relation between the anticoagulant effect and both the prevention of mural thrombosis[20] and the reduction of manifestations of myocardial ischemia after treatment with streptokinase.[21,22] Although heparin in a dose of 12,500 U subcutaneously 2 times per day produces an inadequate anticoagulant effect in virtually all patients over the first 24 hours,[20] this heparin regimen reduced mortality in patients treated with streptokinase both in the GISSI-2/International trials and in the SCATI study.[1,2,27] In contrast, among patients who were treated with rt-PA in the GISSI-2/International trials, there was no effect on the mortality rate in those who received this heparin regimen. However, higher doses of heparin do appear to be effective in preventing reocclusion after rt-PA treatment for acute myocardial infarction. Thus, significantly higher patency rates were demonstrated among rt-PA-treated patients who received high-dose intravenous heparin in 3 well-designed clinical trials (ECSG-6, unpublished observations).[25,26]

Although the interpretation of these seemingly discrepant findings is by no means clear-cut, they could have the following explanation: Heparin in full doses (intravenous bolus of 5,000 U and then continuous intravenous infusion to maintain the APTT at 1.5 times control) is effective in preventing manifestations of rethrombosis (recurrent ischemia) after successful coronary thrombolysis in patients treated with streptokinase[21,22] and in preventing angiographic manifestations of rethrombosis (maintained patency) in patients treated with rt-PA (ECSG-6, unpublished observations).[25,26] Lower doses of heparin (12,500 U subcutaneously 2 times/day) have some beneficial effects in patients treated with streptokinase but not in patients treated with rt-PA. This difference in clinical response (mortality) between the streptokinase- and rt-PA-treated patients to the lower doses of heparin used in the GISSI-2/International trials and SCATI study might be explained by the greater systemic anticoagulant effect produced by streptokinase,[5] which, when augmented by the modest anticoagulant effect of the relative low-dose subcutaneous heparin, results in an antithrombotic effect. Because rt-PA produces a less marked systemic anticoagulant effect, the additional influence of the modest anticoagulant effect obtained from the relatively low dose of heparin used in the GISSI-2/International trials and in the ISIS-3 study may be insufficient to prevent reocclusion, particularly in the critical period soon after thrombolysis. This interpretation is based on the premise that early patency of the infarct-related artery is an important determinant of in-hospital and long-term survival.[29] If this explanation is correct, then heparin should be commenced during or soon after thrombolysis in high doses intravenously and continued for a number of days. Patency studies indicate that such a high-dose heparin approach might be beneficial in patients treated with rt-PA, and subgroup analysis of clinical studies using adjunctive high-dose intravenous heparin after streptokinase[21,22] suggests that additional benefit might be achieved from full-dose heparin over the delayed, lower dose subcutaneous regimen used in the GISSI-2/International trials. The disadvantage of early high-dose adjunctive heparin treatment lies in its potential for serious bleeding, particularly in patients treated with streptokinase. Whether an increase in the incidence of bleeding will outweigh the potentially beneficial effects of early high-dose heparin will have to be resolved by clinical trials and is being addressed by the Global Utilization of Streptokinase and t-PA for Occluded Arteries (GUSTO) trial. In the meantime, it would be reasonable to commence high-dose intravenous heparin in conjunction with rt-PA but to delay heparin treatment for 3 to 4 hours in patients with acute myocardial infarction who are being treated with streptokinase, particularly if a high-dose intravenous regimen is used.

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Role of New Antiplatelet Agents as Adjunctive Therapies in Thrombolysis

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Coronary thrombolysis is the treatment of choice for patients with acute Q-wave myocardial infarcts who have no contraindications to such therapy. However, the time required for thrombolysis and the possibility of reocclusion of the infarct-related artery remain problematic. Herein are described experimental animal studies and clinical evaluations in which attempts have been made to develop adjunctive therapies that, when coupled with available thrombolytic interventions, might shorten the time to thrombolysis and delay or prevent reocclusion. From the studies conducted to date, it is clear that a combined thromboxane synthesis inhibitor and receptor antagonist with a serotonin receptor antagonist and heparin shorten the time to thrombolysis and delay or prevent coronary artery reocclusion in experimental canine models with copper coil-induced coronary artery thrombi. A monoclonal antibody to the platelet glycoprotein IIb/IIIa receptor coupled with tissue plasminogen activator (t-PA) and heparin also shortens the time to thrombolysis and delays or prevents reocclusion in experimental canine models. Thrombin inhibitors, including heparin and synthetic inhibitors, given with t-PA and aspirin, appear to shorten the time to thrombolysis and delay or prevent coronary artery reocclusion in experimental canine models. Aspirin coupled with intravenous streptokinase reduces mortality in patients with presumed acute myocardial infarction, and a combination of heparin and t-PA results in infarct-artery patency more frequently than t-PA without heparin. Data from these studies are encouraging with regard to the possibility of developing effective and relatively safe thrombolytic regimens that shorten the time to thrombolysis and delay or prevent coronary artery reocclusion.

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Coronary thrombolysis has been evaluated extensively as a means to prevent or attenuate pathophysiologic events occurring with acute myocardial infarction. Studies in experimental animals and patients show that the administration of thrombolytic agents early in the course of myocardial infarction reduces infarct size and preserves ventricular function.[1-3] However, the time required for thrombolysis with currently available agents remains longer than desirable, and there is an important risk of coronary artery reocclusion after successful thrombolytic therapy. Thus, it should be useful to identify adjunctive therapy that shortens the time to thrombolysis and prevents coronary artery reocclusion following thrombolytic therapy.

Platelets are activated in response to a variety of substances. Studies from our laboratory as well as others have demonstrated that thromboxane A_2 and serotonin are important mediators of intracoronary platelet activation in experimental preparations of concentrically stenosed canine coronary arteries with endothelial injury.[4-8] Others have shown that the platelet glycoprotein IIb/IIIa platelet receptors are important in platelet binding to fibrin and the development of a thrombus; a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptors enhances thrombolysis in experimental animal models.[9,10] In addition, clinical studies in which aspirin has been combined with selected thrombolytic interventions suggest enhanced thrombolytic protection.[11] This review summarizes current information related to experimental animal and clinical studies that have been performed in an attempt to alter platelet activation and shorten the time to thrombolysis and prevent or delay coronary artery reocclusion after thrombolytic therapy.

STUDIES IN EXPERIMENTAL ANIMAL MODELS

We evaluated whether single or simultaneous administration of thromboxane and serotonin receptor antagonists combined with tissue plasminogen activator (t-PA) and heparin shorten the time to thrombolysis and prevent or delay coronary artery reocclusion after thrombolytic therapy.[12,13] In these studies, coronary thrombi were induced in 26 anesthetized, open-chest dogs by inserting a copper coil into the left anterior descending coronary artery (LAD) (Fig. 1). Coronary artery blood flow velocity was monitored throughout the experiment with a Doppler flow probe placed proximally to the coil. The presence of a thrombus was documented for 30 minutes. Dogs were assigned to 1 of 4 groups: group 1 (n = 8) served as control subjects, receiving a bolus of heparin

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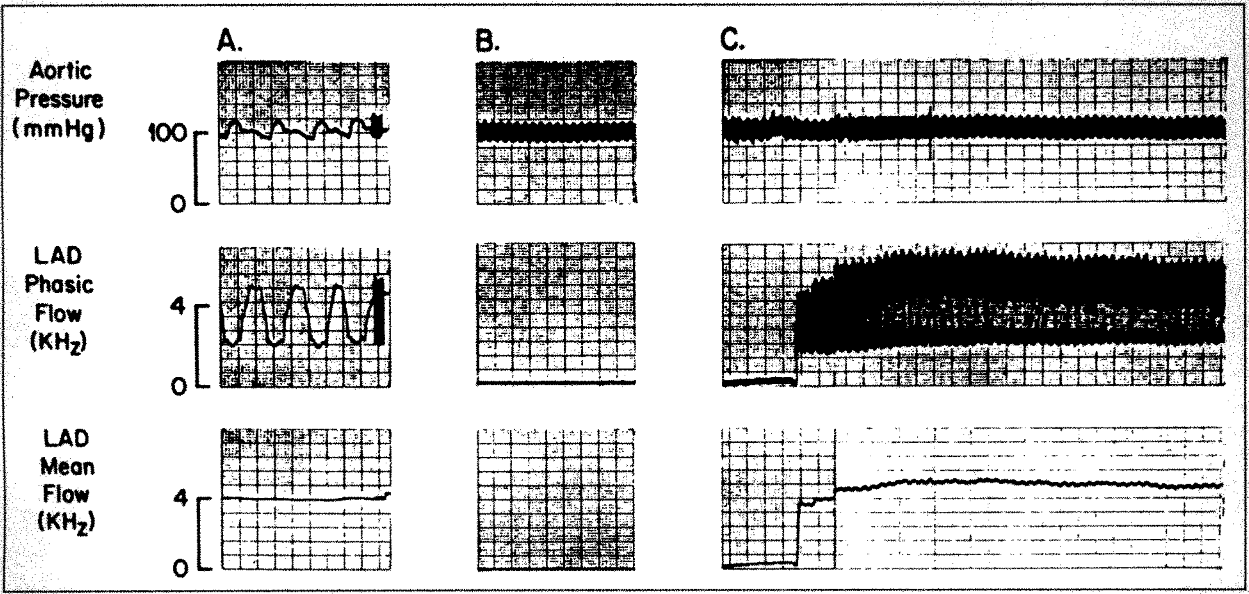

FIGURE 1. Representative tracing of hemodynamic data obtained from a dog treated with heparin, tissue plasminogen activator and thromboxane receptor antagonist SQ29548 and serotonin receptor antagonist LY53857 in combination. *A*, baseline measurements (paper speed, 25 mm/s). *B*, after placement of the copper coil into the left anterior descending coronary artery (LAD) and thrombus formation (paper speed, 25 mm/min). *C*, administration of tissue plasminogen activator caused lysis of the thrombus and restoration of blood flow that showed a stable and constant pattern throughout the experimental period (paper speed, 25 mm/min). (See text for details.) (Reproduced with permission of the American Heart Association, *Circulation*.[12])

(200 U/kg) and of t-PA (80 μg/kg), followed by a continuous infusion (8 μg/kg·min) for ≤90 minutes or until reperfusion was achieved. Group 2 (n = 10) received, immediately before heparin and t-PA, an intravenous bolus of 0.4 mg/kg of a thromboxane receptor antagonist (SQ29548, Squibb Pharmaceuticals, Princeton, New Jersey) and 0.2 mg/kg of a serotonin receptor antagonist (LY53857, Eli Lilly Pharmaceuticals, Indianapolis, Indiana). Group 3 (n = 7) received, before heparin and t-PA, an intravenous bolus of the thromboxane receptor antagonist alone (0.4 mg/kg). Group 4 (n = 7) received, before heparin and t-PA, an intravenous bolus of the serotonin receptor antagonist alone (0.2 mg/kg). After thrombolysis, all dogs were monitored for 90 minutes or until a persistent reocclusion occurred.

Treatment with a combination of the thromboxane and serotonin receptor antagonists markedly shortened the time required to lyse coronary artery thrombi, from 46 ± 7 to 15 ± 3 minutes in groups 1 and 2 animals, respectively ($p < 0.01$, Fig. 2). Neither receptor antagonist alone was as effective in accelerating thrombolysis. In the animals treated with t-PA and heparin alone (group 1), repeated cycles of gradual occlusions followed by spontaneous restorations of flow (i.e., cyclic flow variations) were observed before persistent reocclusion occurred within 17 ± 5 minutes (Fig. 3). Coadministration of thromboxane and serotonin receptor antagonists before heparin and t-PA prevented or delayed reocclusion in each of the group 2 dogs that were successfully reperfused (Table I). Neither the thromboxane nor serotonin receptor antagonist alone was effective in preventing cyclic flow variations and reocclusion. Thus, thromboxane and serotonin receptor antagonists in combination enhance the thrombolytic effect of t-PA, probably by preventing further platelet activation and by their incorporation into the thrombus during lytic therapy. The combination of these 2 receptor antagonists appears to be effective in preventing or delaying reocclusion after discontinuation of t-PA in this experimental model.

EFFICACY OF A COMBINED THROMBOXANE SYNTHESIS INHIBITOR AND RECEPTOR ANTAGONIST IN ENHANCING THROMBOLYSIS AND DELAYING OR PREVENTING REOCCLUSION

Seventy anesthetized, open-chest dogs in whom coronary artery thrombi were induced with a copper coil, as described earlier, were evaluated.[14] In these studies, the efficacy of a combined thromboxane synthesis inhibitor and receptor antagonist (ridogrel, Janssen Pharmaceutical, Beerse, Belgium) in combination with t-PA and heparin were evaluated and compared to that of t-PA and heparin alone in enhancing thrombolysis. In these studies, ridogrel added to t-PA and heparin markedly shortened the time to thrombolysis in treated dogs from approximately 45 to 12 minutes (Fig. 4).[14] In addition, coronary artery reocclusion after discontinuation of the t-PA was either prevented or markedly delayed by combined thromboxane synthesis inhibition and receptor antagonism (Fig. 4). In these studies, we identified an increase in distal coronary artery prostacyclin concentration after the administration of ridogrel, presumably as a result of shunting cyclic endoperoxides toward prostacyclin after the administration of the combined thromboxane synthesis inhibitor and receptor antagonist. Increases in thromboxane were prevented by ridogrel, and in vivo assess-

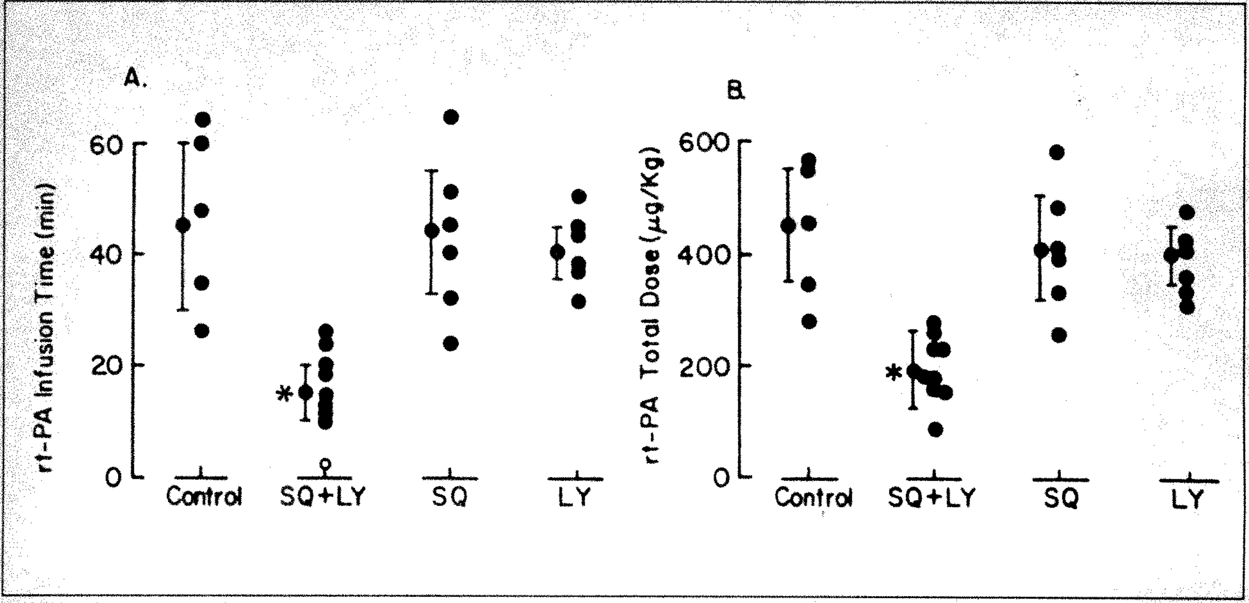

FIGURE 2. *A*, plot of time of recombinant tissue-type plasminogen activator (rt-PA) infusion (i.e., time to achieve thrombolysis) in dogs with coronary thrombosis receiving heparin (group 1); heparin and thromboxane receptor antagonist SQ29548 (SQ) and serotonin receptor antagonist LY53857 (LY) in combination (group 2); heparin and SQ alone (group 3); and heparin and LY alone (group 4). Only the administration of SQ and LY in combination significantly decreased the time necessary to achieve effective thrombolysis (defined as left anterior descending coronary artery blood flow ≥70% of baseline value). $^*p < 0.01$ by *t* test with Bonferroni's correction. *B*, plot of total dose of rt-PA necessary to lyse the intracoronary thrombus in dogs receiving heparin (200 U/kg) (group 1); heparin and SQ and LY combination (group 2); heparin and SQ alone (group 3); and heparin and LY in combination (group 4). The latter combination significantly reduced the dose of rt-PA necessary to achieve reperfusion. $^*p < 0.02$ by *t* test with Bonferroni's correction. Data are expressed as mean ± 95% confidence interval. (Reproduced with permission from the American Heart Association, *Circulation*.[12])

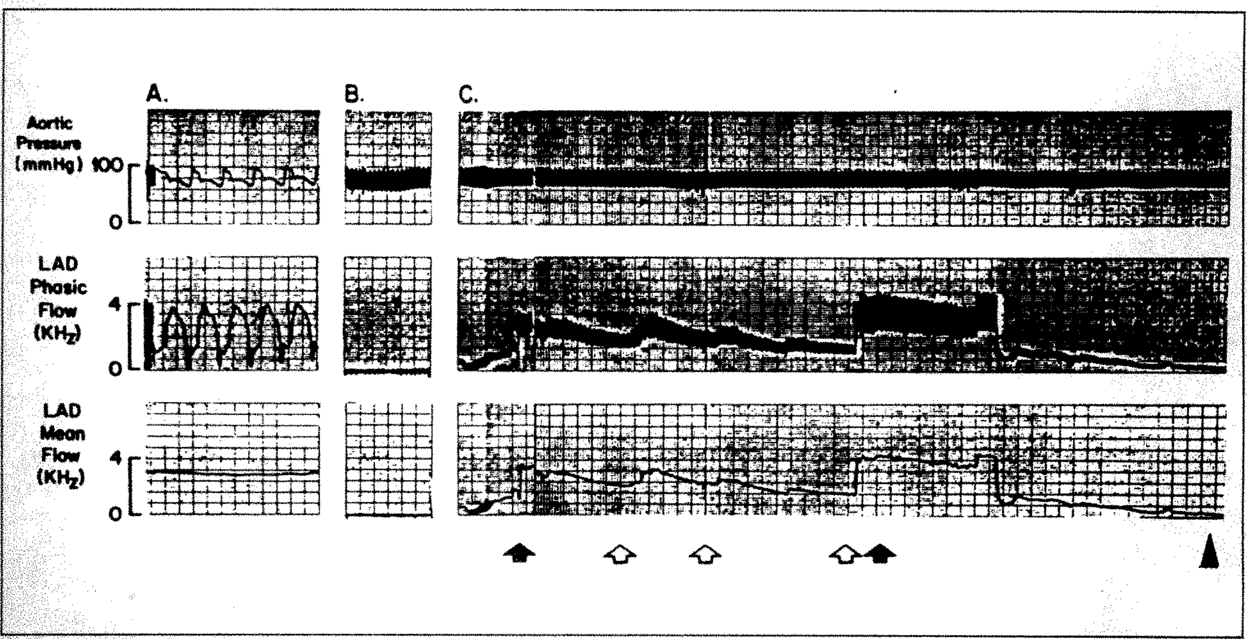

FIGURE 3. Representative tracing of hemodynamic data obtained from a dog treated with heparin and tissue plasminogen activator only (group 1). *A*, before placement of the copper coil into the left anterior descending coronary artery (LAD), coronary blood flow shows a stable and constant pattern (paper speed, 25 mm/s). *B*, after positioning of the coil, LAD blood flow decreased to almost unrecordable values (paper speed, 25 mm/min). *C*, during infusion of tissue plasminogen activator, the intracoronary thrombus was progressively lysed and blood flow through the LAD was restored *(closed arrow)*. The *arrow* indicates the time when the infusion of tissue plasminogen activator was discontinued. Despite the administration of 200 U/kg of heparin, LAD blood flow showed a typical pattern of gradual decrease of flow *(open arrows)*, followed by spontaneous restoration of blood flow *(closed arrow)* until a reocclusion occurred *(arrowhead)* (paper speed, 25 mm/min). (Reproduced with permission from the American Heart Association, *Circulation*.[12])

TABLE I Reocclusion Time and Activated Coagulation Time (ACT) in Dogs After Thrombolysis With Tissue Plasminogen Activator

Group No.	Reocclusion Time	Base	Reperfusion	90 Minutes Reperfusion or Reocclusion
1	17 ± 5 (0)*	96 ± 6	207 ± 15	199 ± 12
2	>90 (9/9)*†	107 ± 7	199 ± 14	193 ± 19
3	31 ± 29 (1/6)*	104 ± 7	212 ± 21	220 ± 23
4	27 ± 31	100 ± 13	227 ± 24	204 ± 19

* Numbers in parentheses indicate dogs in whom the treatment prevented reocclusion after thrombolysis.

† p <0.005 versus groups 1, 3, and 4 by Fisher's exact test.

Reocclusion time (minutes) was defined as the time elapsed between reperfusion and the occurrence of a persistent reocclusion.

ACT (seconds) was measured at baseline, at the moment of reperfusion, and after 90 minutes of reperfusion or at the moment of reocclusion. See text for details.

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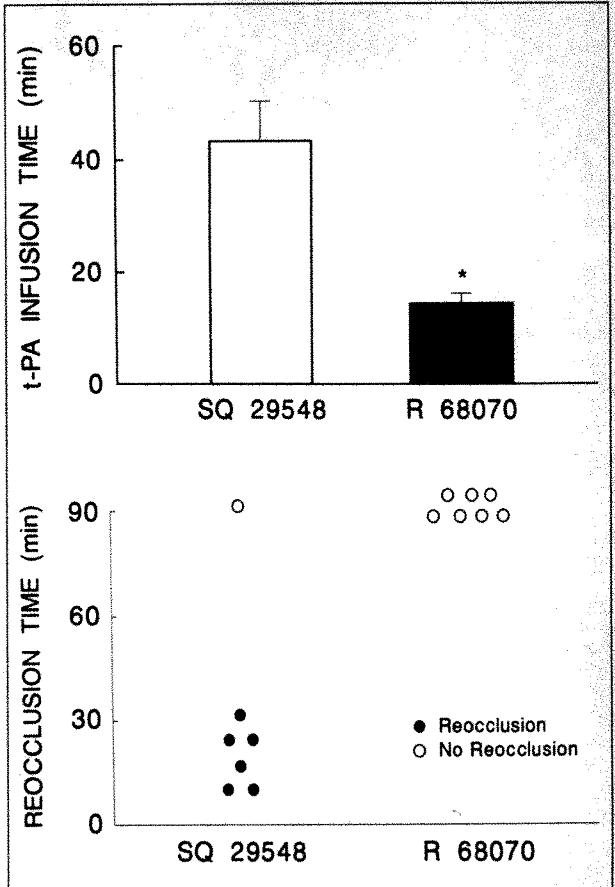


FIGURE 4. ***Top*, the reduction in the time required for thrombolysis when tissue plasminogen activator (t-PA) is given to anesthetized, open-chest dogs with a copper coil-induced coronary artery thrombus with a combined thromboxane synthesis inhibitor and receptor antagonist (R68070). The animals were treated with t-PA, heparin, and either a thromboxane receptor antagonist (SQ29548) or a combined thromboxane synthesis inhibitor and receptor antagonist (R68070). *p <0.01. *Bottom*, the administration of a combined thromboxane synthesis inhibitor and receptor antagonist (R68070) after tissue plasminogen activator and heparin delayed or prevented coronary artery reocclusion in anesthetized, open-chest dogs when a copper coil had been used to induce thrombosis. In contrast, the administration of a thromboxane receptor antagonist (SQ29548) by itself after tissue plasminogen activator and heparin failed to delay or prevent coronary artery reocclusion.**

ments of platelet aggregation demonstrated that platelet aggregation in response to a thromboxane mimetic (U46619) was prevented by the in vivo administration of ridogrel.[14]

COMPARATIVE EFFECTS OF ASPIRIN, A SYNTHETIC THROMBIN INHIBITOR, AND A MONOCLONAL ANTIPLATELET GLYCOPROTEIN IIb/IIIa ANTIBODY

The comparative effects of intravenous aspirin, the synthetic thrombin inhibitor, (2R, 4R)-4-methyl-1-[N^2-(3-methyl-1,2,3,4-tetrahydro-8-quinolinesulfonyl)-L-arginyl]-2-piperidinecarboxylic acid monohydrate (argatroban), and F(ab′)2 fragments of the monoclonal antibody, 7E3, against platelet glycoprotein IIb/IIIa receptors (7E3-F[ab′]2) on thrombolysis, reocclusion and bleeding associated with 0.45 mg/kg of body weight bolus injections of recombinant t-PA were studied in a canine coronary artery thrombosis model.[15] In these studies, coronary artery thrombosis was induced by mechanical damage to the endothelium. Total coronary artery occlusion was confirmed by coronary arteriography. Four groups of animals were studied: group 1 animals were pretreated with 17 mg/kg of intravenous aspirin (n = 6); group 2 was pretreated with 200 μg/kg per minute of intravenous argatroban for 60 minutes (n = 5); group 3 was pretreated with aspirin and argatroban (n = 5); and group 4 was pretreated with 0.8 mg/kg of intravenous 7E3-F(ab′)2 (n = 5). In group 1, reperfusion occurred in 4 of 6 dogs, but did not persist. Reperfusion occurred in 4 of 5 dogs in group 2, persisting in 1. In group 3, reperfusion occurred in all 5 dogs and persisted in 4; and in group 4, reperfusion occurred in 4 of 5 dogs and persisted in 2 (Fig. 5, Table II). Reperfusion in group 3 animals was significantly higher than in combined groups 1 and 2, whereas the time to reperfusion was significantly shorter in the groups receiving argatroban than in the aspirin-treated group (25 vs 55 minutes, p = 0.04) (Fig. 5). There were significant differences between group 3 and 4 animals in the frequency of reperfusion. Bleeding times were prolonged from 4 ± 1 to 5 ± 3 minutes at 60 minutes in group 1; 9 ± 11 minutes in group 2; 12 ± 11 minutes in group 3; and 27 ± 8 minutes in group 4 animals. One hour after the infusion, bleeding times were 5.0 ± 0.9, 5.2 ± 1.3, 14 ± 9.2, and 26 ± 9 minutes, respectively.

These data suggest that argatroban accelerates coronary thrombolysis with t-PA and that the combination of aspirin and argatroban delays or prevents coronary artery reocclusion. These effects were achieved with less pronounced prolongation of the bleeding time than was observed with a potent antiplatelet glycoprotein IIb/IIIa receptor antibody, and suggest that inhibition of platelet activation with aspirin in combination with a short-lived synthetic thrombin inhibitor may constitute an alterna-

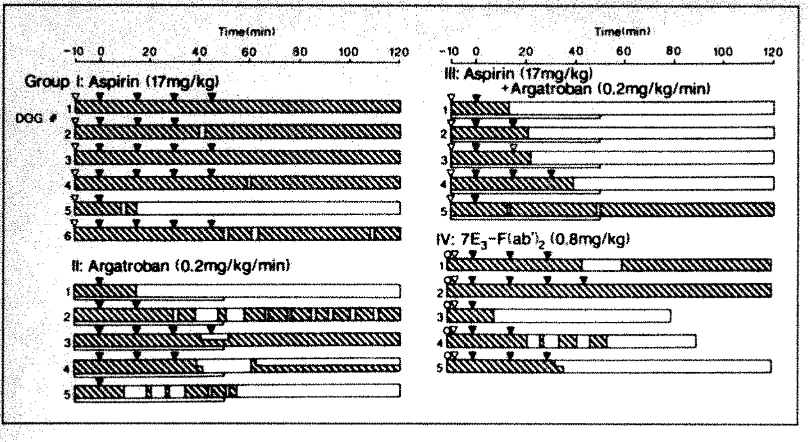


FIGURE 5. Schematic representation of the coronary artery patency status in dogs receiving bolus injections of 0.45 mg/kg of tissue plasminogen activator in association with administration of aspirin, argatroban or 7E3-F(ab')2. *Open box,* continuous intravenous infusion of argatroban. *Open bars* represent patency and *hatched bars* occlusion of the coronary artery. The *half-open bar* represents partial reflow. (Reproduced with permission from *J Am Coll Cardiol.*[15])

TABLE II Effects of Aspirin, Argatroban and 7E3-F(ab')2 on Coronary Artery Recanalization and Reocclusion With Recombinant Tissue-Type Plasminogen Activator

		Blood Flow (ml/min)		Coronary Patency[*] (frequency)				Reperfusion[†]			
									Time (min)		
Experimental Group	No.	Baseline	Poststenotic	PO	RR	CR	PP	Total No.	Mean ± SD	Median	Range
I: aspirin	6	16 ± 5	6.3 ± 1.1	2	2	2	0	4/6	40 ± 20	55	14–120
II: argatroban	5	15 ± 3	6.0 ± 1.7	1	0	3	1[‡]	4/5	23 ± 14	28	7–120
III aspirin + argatroban	5	12 ± 4	5.1 ± 0.5	0	0	1	4[§]	5/5	24 ± 11	21	14–39
IV: 7E3-F(ab')2	5	13 ± 5	5.0 ± 1.8	1	1	1	2[‖]	4/5	27 ± 17	33	9–120

[*] p = 0.036 for significant differences by Kruskal-Wallis nonparametric analysis of variance.
[†] Values are mean ± standard deviation (SD) in responsive animals, and the median and range are values for the total group.
[‡] p = not significant versus aspirin.
[§] p = 0.009 versus pooled aspirin and argatroban groups, p = 0.064 versus argatroban and p = 0.008 versus aspirin.
[‖] Difference not significant versus pooled aspirin and argatroban and versus aspirin + argatroban. Unless indicated, values are mean ± SD.
CR = cyclic reflow; PO = persistent occlusion; PP = persistent patency; RR = reflow and reocclusion.
(Reproduced with permission from *J Am Coll Cardiol.*[15])

tive approach to improving coronary artery patency with thrombolytic therapy.[15]

CLINICAL EVALUATIONS

Second International Study of Infarct Survival (ISIS–2): A multicenter, randomized trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 patients with suspected myocardial infarction showed that intravenous streptokinase alone, aspirin alone, and, even more prfoundly, the combination of intravenous streptokinase and aspirin reduce mortality when given within the first 24 hours of symptom onset to patients with suspected myocardial infarction (Fig. 6).[11]

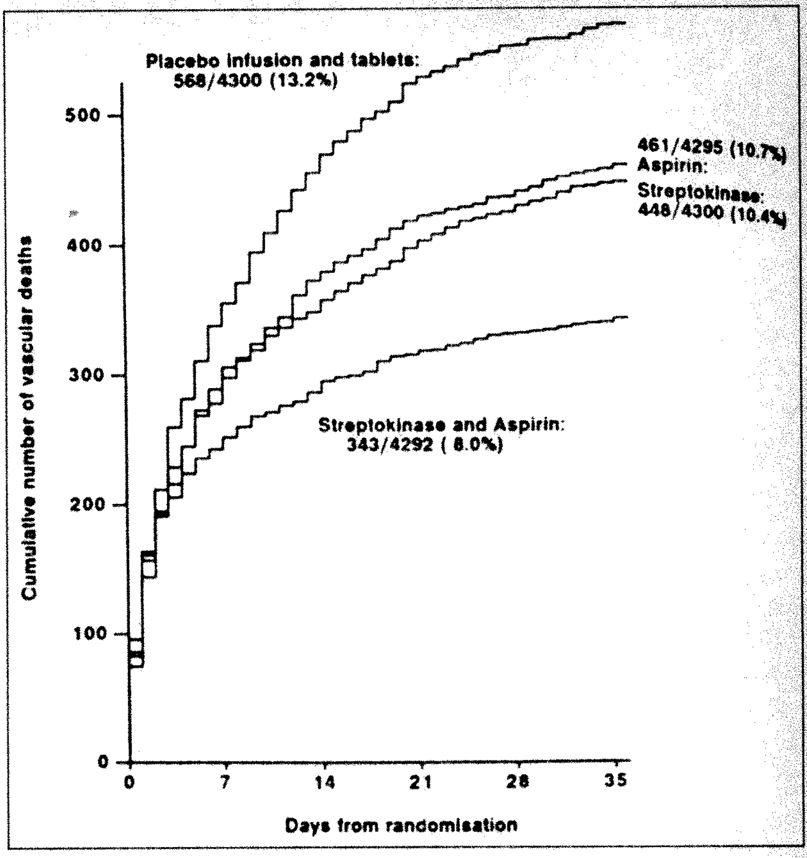
These studies identify the importance of the administration of a platelet-active agent, such as aspirin, in potentiating the thrombolytic effect of streptokinase with regard to its ability to reduce mortality. The dose of aspirin used was 160 mg/day, and it was given immediately after the patient was identified. Bleeding risks were more frequent in patients receiving intravenous streptokinase. These data have served to encourage the administration of aspirin with thrombolytic intervention, and the dose used is usually one-half to 1 aspirin tablet per day.

The Heparin-Aspirin Reperfusion Trial: Recently, the Heparin-Aspirin Reperfusion Trial (HART) was completed. In this study, patients with acute myocardial infarction presenting within 6 hours of symptom onset received t-PA and were randomized to immediate additional therapy with intravenous heparin or oral aspirin.[16] Patients receiving t-PA and heparin had an infarct-related artery patency rate of 82% on initial angiography performed at a mean of 18 hours. In contrast, only 52% of patients receiving t-PA and aspirin had a patent infarct-related artery ($p < 0.0001$). Follow-up angiography at 7 to 10 days revealed equivalent patency rates of approximately 90%. The frequency of hemorrhagic and recurrent ischemic events was similar for the adjunctive strategies. Ross et al[16] concluded that these studies demonstrate that the thrombolytic effect of t-PA is markedly potentiated by the concomitant administration of intravenous heparin. It should be emphasized, however, that the dose of aspirin used was not large enough to guarantee suppression of thromboxane synthesis, especially in a clinical setting where systemic catecholamine concentration was almost certainly markedly elevated.

DISCUSSION

These studies indicate that the thrombolytic efficacy of the available thrombolytic interventions may be enhanced in experimental animals by a combined thromboxane synthesis inhibitor and receptor antagonist and with these agents and a serotonin receptor antagonist. A

FIGURE 6. Beneficial effect of combining streptokinase and aspirin in reducing mortality during a 35-day period after the administration of thrombolytic therapy to patients with suspected myocardial infarction. Aspirin and streptokinase alone also exerted a beneficial effect, but the magnitude of the effect was potentiated by combining streptokinase and aspirin. (Reproduced with permission from *Lancet*.[11])



monoclonal antibody to the platelet glycoprotein IIb/IIIa receptor (platelet-fibrinogen receptor) exerts the same beneficial effects in experimental animals. Concomitant administration of aspirin and heparin potentiates the thrombolytic effects of t-PA and streptokinase in humans. These adjunctive strategies combined with thrombolytic therapy appear to enhance reperfusion frequency and delay or prevent coronary artery reocclusion. In canine models, selected platelet-active therapies markedly shorten the time to thrombolysis when given in combination with t-PA, and they will most likely exert similar effects with at least selected other thrombolytic interventions as well.

These results are not surprising, in that platelets adhere at sites of endothelial injury when the subendothelium is exposed, such as occurs with atherosclerotic plaque fissuring and ulceration. The accumulation of platelets at such sites is associated with local increases in thromboxane A_2 and serotonin concentrations, and, most likely, adenosine diphosphate and platelet activating factor.[6,17-19] In addition, Fitzgerald demonstrated that the administration of the thrombolytic interventions, streptokinase and t-PA, stimulates platelet activation and thromboxane A_2 release.[20] Thus, one would anticipate that therapeutic strategies that interfere with the effects of thromboxane A_2 and serotonin would enhance thrombolysis and delay or prevent coronary artery reocclusion. The clinical observation that aspirin potentiates the thrombolytic effect of streptokinase in reducing subsequent mortality in patients is not unexpected based on the experimental data that are available.[4-8,11,17-20] It remains to be determined whether combined thromboxane synthesis inhibition and receptor antagonism and a serotonin receptor antagonist, the monoclonal antibody to the platelet glycoprotein IIb/IIIa receptor or other antiplatelet antibodies, antagonists, or synthetic peptides that block glycoprotein IIb/IIIa or Ib platelet receptors will shorten the time to thrombolysis in patients. An antithrombin intervention should be coupled with a thrombolytic intervention; heparin appears to be acceptable but, in the future, more specific thrombin antagonists might be used with a thrombolytic agent alone or coupled with heparin to enhance the thrombolytic effect. Additional data related to thrombin inhibitors, alone and in combination, will be forthcoming from clinical studies performed in the near future.

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Role of New Anticoagulants as Adjunctive Therapy During Thrombolysis

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Procoagulant activity may persist during coronary thrombolysis and result in either delay in the time to recanalization or recurrent thrombosis. Although heparin and aspirin form the mainstay of current therapy, recurrent thrombosis occurs despite adjunctive heparin therapy during thrombolysis. Newer agents that inhibit thrombin by antithrombin III-independent mechanisms, or that inhibit earlier steps in the coagulation cascade, have been shown to be effective in the experimental preparation of coronary thrombolysis. Because heparin-antithrombin III is a relatively inefficient inhibitor of thrombin bound to fibrin, agents such as hirudin or small peptide inhibitors of the thrombin-active site appear to be more effective inhibitors of clot-associated thrombin activity. Inhibition of early steps in the coagulation cascade with the inhibitor of tissue factor-factor VIIa complex, or with activated protein C, also appears to be an effective anticoagulant strategy. In experimental preparations all of these agents have shown superiority in preventing recurrent thrombosis compared with heparin, and in some cases they appear to accelerate the rate of clot lysis.

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The initiation and progression of coronary artery thrombosis are determined by a dynamic balance between procoagulant factors that result in fibrin deposition and platelet aggregation, and fibrinolytic activity that induces plasmin-mediated clot lysis. The goal of pharmacologic plasminogen activation is to shift this balance by markedly increasing fibrinolytic activity, thus promoting clot lysis. However, procoagulant activity persists during thrombolysis and may result in either delay in the time to recanalization or recurrent thrombosis.[1] Presumably, the inhibition of this persistent procoagulant activity accounts for the increased rate of recanalization and decreased rate of recurrent thrombosis observed with adjunctive heparin therapy during thrombolysis.[2-4] Although heparin and aspirin form the mainstay of current therapy, recent data regarding potential mechanisms responsible for persistent or increased procoagulant activity during thrombolysis suggest that new strategies for the inhibition of thrombin or other procoagulants may have advantages over currently available agents.

MECHANISMS FOR INCREASED PROCOAGULANT ACTIVITY DURING THROMBOLYSIS

The initial success of coronary thrombolysis depends on the extent to which plasminogen bound to fibrin is activated to induce fibrinolysis, and the extent to which recurrent fibrin deposition and rethrombosis are inhibited. Multiple mechanisms for persistent procoagulant activity during thrombolysis have been identified and may be important determinants of rethrombosis. These include persistent expression of procoagulant factors associated with arterial wall injury,[5,6] procoagulant effects of the thrombus itself,[7,8] alterations in the regulation of coagulant and fibrinolytic activity by endothelium,[9] and induction of procoagulant activity in plasma by activation of plasminogen (Fig. 1).[1,10-12] Whatever the initial stimulus, increased procoagulant activity leads to elaboration of thrombin, which induces fibrin formation and polymerization as well as platelet activation. Recurrent thrombosis may also be due to factors that inhibit fibrinolytic activity, thus attenuating fibrin lysis.[13]

Current strategies for inhibiting procoagulant activity during thrombolysis include inhibition of thrombin and factor Xa with heparin, and inhibition of platelet activity with aspirin. Recent clinical trials have underscored the role of adjunctive heparin and aspirin therapy during thrombolysis by demonstrating increased coronary patency with heparin therapy in patients treated with tissue plasminogen activator (t-PA)[2,3] and improved survival in patients treated with streptokinase and aspirin or hepa-

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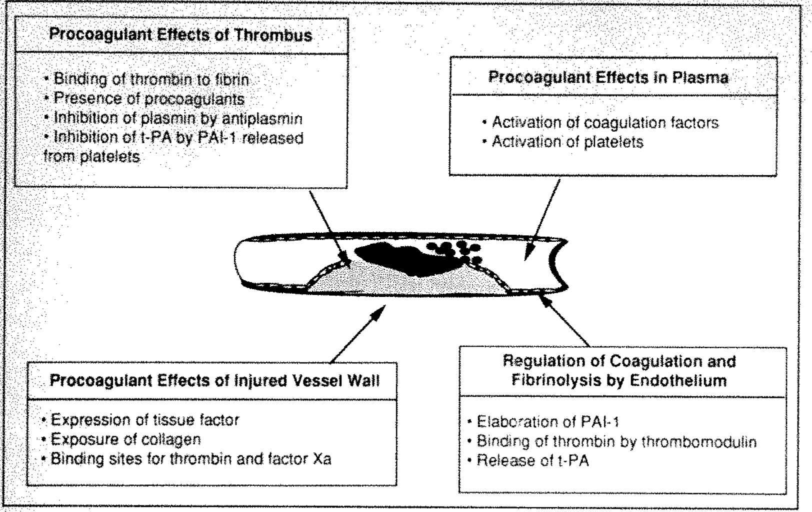
Procoagulant Effects of Thrombus
• Binding of thrombin to fibrin
• Presence of procoagulants
• Inhibition of plasmin by antiplasmin
• Inhibition of t-PA by PAI-1 released from platelets
Procoagulant Effects in Plasma
• Activation of coagulation factors
• Activation of platelets
Procoagulant Effects of Injured Vessel Wall
• Expression of tissue factor
• Exposure of collagen
• Binding sites for thrombin and factor Xa
Regulation of Coagulation and Fibrinolysis by Endothelium
• Elaboration of PAI-1
• Binding of thrombin by thrombomodulin
• Release of t-PA

FIGURE 1. Potential mechanisms for increased procoagulant activity during thrombolysis. t-PA = tissue plasminogen activator; PAI-1 = plasminogen activator inhibitor type 1.

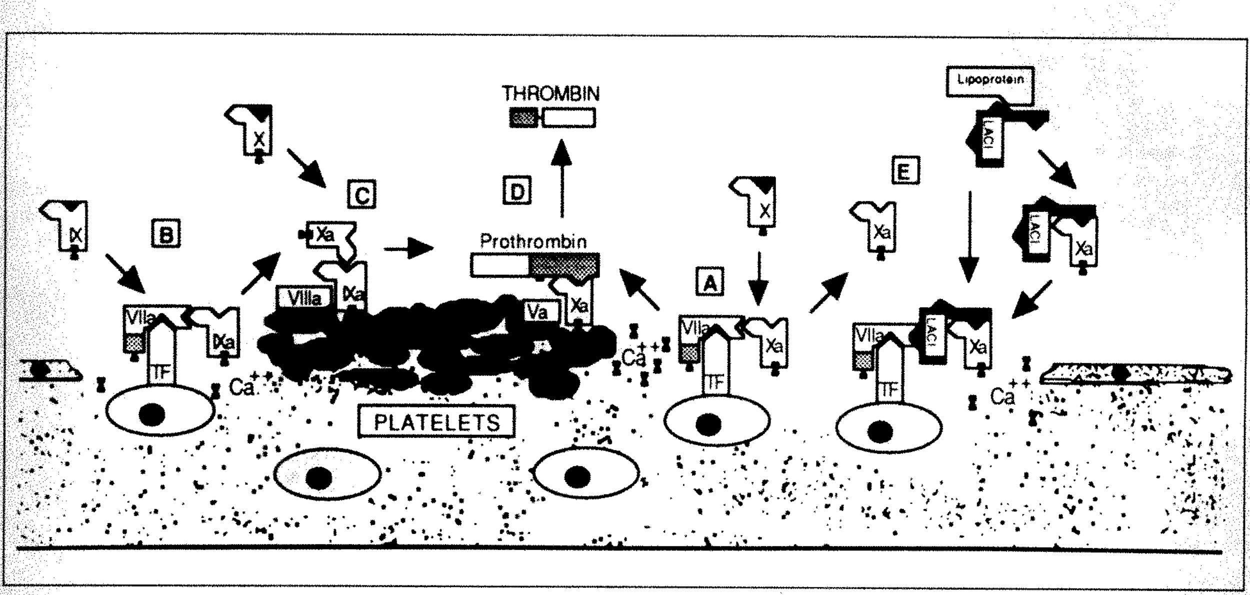

FIGURE 2. Potential mechanisms for activation of the coagulation system in deep arterial wall injury. This scheme emphasizes the role of tissue factor (TF) and its regulation by lipoprotein-associated coagulation factor. *A*, TF exposed in the subendothelium initiates coagulation by binding with factor VII or VIIa, accelerating the activation of factor X. *B*, TF-factor VIIa complex (VIIIa) can also catalyze activation of factor IX. *C*, activated factor IX (IXa) associates with factor VIIIa in a complex, most likely on cell phospholipid membranes, to catalyze the activation of factor X. *D*, factor Xa forms a complex with factor Va (prothrombinase complex) on phospholipid surface membrane of cells, such as aggregated platelets, and activates prothrombin to thrombin. *E*, TF-mediated activation of the coagulation system is regulated by lipoprotein-associated coagulation inhibitor (LACI), which is associated with lipoproteins in plasma. LACI binds to and inhibits either free factor Xa or factors Xa and VIIa when they are associated with the TF factor VIIa-Xa complex. All of these reactions in the formation of complexes require the presence of calcium and phospholipid. (Reproduced with permission from Eisenberg PR. *Coronary Artery Disease* 1990;1:159–165.)

rin,[14,15] compared with that in patients treated with the fibrinolytic agent alone. Despite continuous infusion of heparin, recurrent thrombosis may occur in 20 to 40% of patients treated with t-PA.[16,17] However, an analysis of several trials by Raynaud and Desveaux[18] revealed that reocclusion occurs in approximately 16% of patients treated with t-PA, similar to that seen with other available thrombolytic agents.

It is also known that aspirin-inhibited platelets can be activated by thrombin.[19,20] In experimental preparations of arterial thrombolysis, recently developed antithrombin agents have been shown to be more effective than heparin in inhibiting rethrombosis, and they appear to accelerate the rate of clot lysis and inhibit platelet deposition.[21–23] Although development of thrombin inhibitors has been a major focus of current investigations, inhibition of procoagulant factors that lead to elaboration of thrombin may be as effective and more efficient than inhibiting thrombin activity and may be less likely to cause bleeding complications resulting from total inhibition of thrombin activity. Because multiple mechanisms exist for increased procoagulant activity during thrombolysis, the value of

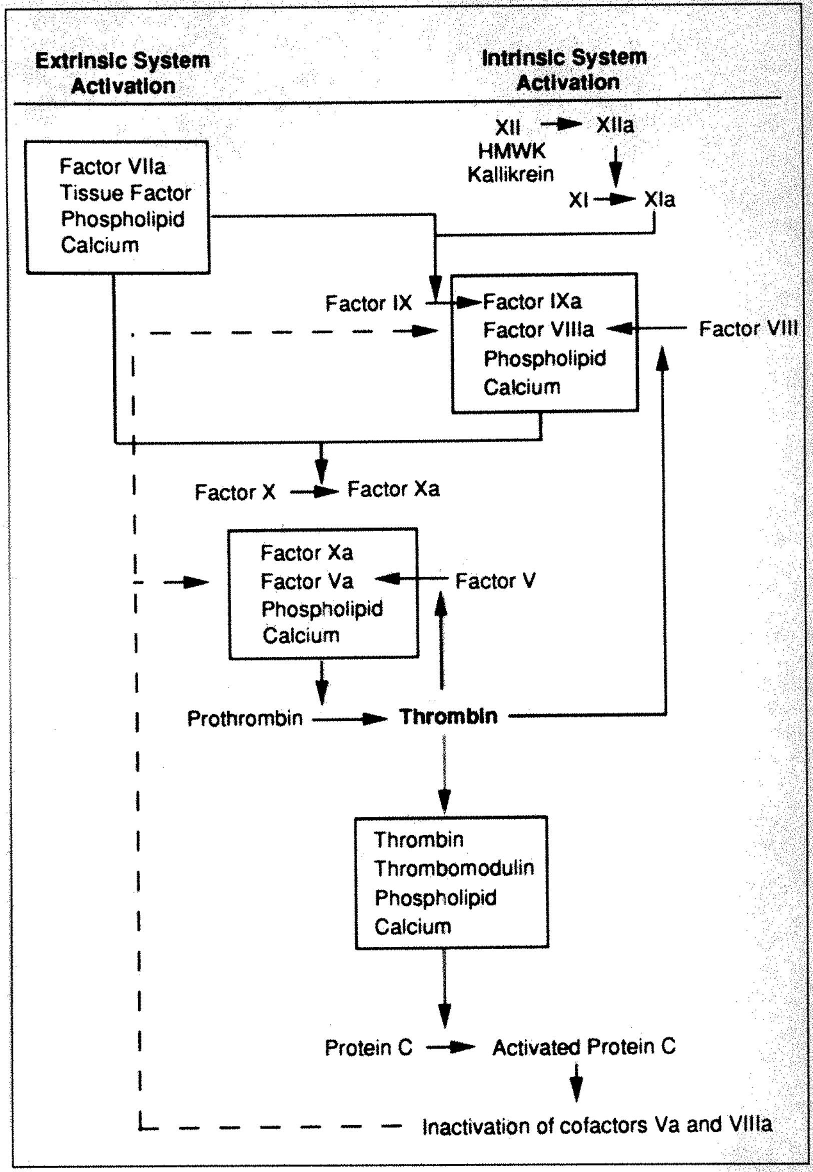

FIGURE 3. Mechanisms by which thrombin can exert positive or negative feedback on activation of the coagulation system in the steps involving vitamin K-dependent factors. The vitamin K-dependent factors and their associated cofactors are shown. Thrombin exerts positive feedback by activating factor VIII, the cofactor for factor IXa, or it may activate factor V, accelerating the activation of prothrombin by factor Xa-Va complex. Thrombin may also initiate anticoagulant mechanisms by activating protein C, which proteolytically inactivates factor Va and VIIIa. HMWK = high-molecular-weight kininogen. (Reproduced with permission from Eisenberg PR. *Coronary Artery Disease* 1990;1:159–165.)

specific agents may vary depending on the factors responsible for procoagulant activity, and the specific fibrinolytic agent used may vary among patients.

PROCOAGULANT EFFECTS OF THE INJURED VESSEL WALL

Recent data suggest that the primary procoagulant in arterial wall injury is tissue factor. Tissue factor, the lipoprotein procoagulant in tissue thromboplastin, appears to be present in the subendothelium of arteries, and its concentration may be increased in atherosclerotic plaque.[6,24,25] Tissue factor is expressed on the membranes of multiple cell types, and initiates activation of the extrinsic pathway by serving as a cofactor to factor VIIa, leading to the activation of factor X (Fig. 2).[26] Because tissue factor and factor VIIa may activate factor IX,[27] both the classic intrinsic and extrinsic factors of coagulation may be activated by exposure of tissue factor to coagulation factors circulating in plasma. Recently, an inhibitor of tissue factor-factor VIIa complex, referred to as the lipoprotein-associated coagulation inhibitor (LACI), has been identified.[28,29] This agent inhibits activation of factor X by the tissue factor-factor VIIa complex and the activity of factor Xa (Fig. 2). Activation of the coagulation cascade in vivo also depends on the assembly of activated coagulation factors in complexes on cell membranes.[30] These complexes appear to have a similar configuration, in which the vitamin K-dependent serine protease associates with a cofactor in the presence of calcium on phospholipid membranes, an example being the "prothrombinase complex" of factor Xa-factor Va that activates prothrombin (Fig. 3). The importance of these complexes is that they exhibit greater enzymatic activity toward their substrates than the activated serine protease alone. Thus, one strategy being investigated for inhibiting coagulation is to interfere with formation of the

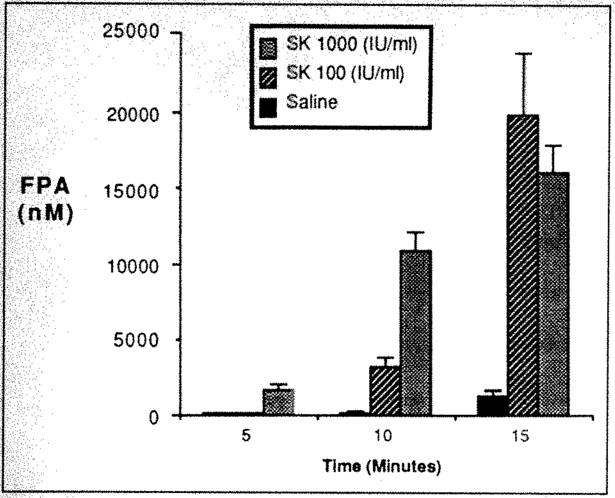

FIGURE 4. Concentrations of fibrinopeptide A (FPA) at 5, 10 and 15 minutes in nonanticoagulated blood incubated at 37°C with streptokinase (SK), either at 100 IU/ml *(hatched bars)* or 1,000 IU/ml *(gray bars)*, compared with the concentrations in blood incubated without SK. Significantly greater concentrations of FPA were measured at each time point in the presence of SK, consistent with increased thrombin activity compared with that in blood incubated without SK ($p \leq 0.001$ by analysis of variance for repeated measures). In blood incubated with 1.0 U/ml of heparin, the concentration increased only minimally when incubated with SK (1,000 IU/ml); the maximal increase was 38.2 ± 4.7 nM at 15 minutes.

protease-cofactor complex. Although specific agents have not been extensively tested, preliminary results demonstrating anticoagulant properties of a peptide that inhibits the membrane binding-portion of the factor X molecule suggest that such a strategy may be successful.[31]

Coronary thrombi are typically platelet-rich, in part due to physical forces, such as shear stress, which results in increased platelet aggregation.[20] In addition, thrombin is a potent platelet agonist and appears to play a primary role in platelet activation and aggregation in response to arterial wall injury. Thrombin also binds to subendothelial matrix, and is protected from inhibition by antithrombin III when bound to matrix proteins.[32] Activated platelets release factor Va and provide a membrane binding site for the factor Xa-Va complex,[33] potentiating arterial thrombosis. Thus, in coronary thrombosis, tissue factor-mediated activation of the extrinsic pathway of coagulation leads to elaboration of thrombin, which amplifies the coagulant response by activating cofactors V and VIII and by activating platelets.

Because expression of tissue factor appears to be a primary stimulus, there has been considerable interest in the use of LACI as an anticoagulant. Recently, LACI has been cloned and expressed in quantities sufficient for use as adjunctive therapy in experimental preparations of coronary thrombolysis. In a canine preparation, administration of LACI after coronary thrombolysis with t-PA decreased the frequency of reocclusion compared with that after adjunctive therapy with heparin (Haskel EJ et al, unpublished observations). Thus, LACI appears to be an attractive anticoagulant because it inhibits the initial steps of coagulation and factor Xa, the key step in activation of the coagulation cascade.

Thrombin-activated protein C is an important natural anticoagulant that acts by inhibiting cofactors V and VIII (Fig. 3). Recently, activated recombinant protein C has been developed for use as an anticoagulant; this agent was found to inhibit platelet dependent thrombosis in a primate arterial shunt preparation,[34] and its infusion significantly inhibited platelet deposition and fibrin formation without significantly altering hemostatic variables. Presumably, the anticoagulant action of activated protein C reflects its ability to attenuate thrombin formation.

PROCOAGULANT EFFECTS OF PLASMINOGEN ACTIVATION IN PLASMA

Thrombin activity increases in patients given t-PA or streptokinase for myocardial infarction, judging from increases in the plasma concentration of fibrinopeptide A, a peptide cleaved from fibrinogen by thrombin.[1,10,35] Concentrations increase in patients with myocardial infarction within 30 minutes of initiation of an infusion of 750,000 IU of streptokinase, and decrease after intravenous heparin.[10] Incubation of nonanticoagulated whole blood with pharmacologic concentrations of streptokinase induces similar marked increases in thrombin activity that can be inhibited by heparin (Fig. 4). However, high concentrations of heparin are required, relative to those typically achieved in patients with an intravenous bolus.[11] The intensity of thrombin activity induced is less marked with t-PA, which is likely due to the preferential activation of plasminogen bound to fibrin as opposed to circulating plasminogen. The extent to which the procoagulant activity induced by plasminogen activation increases clotting appears to be mediated by the extent of fibrinogen degradation and elaboration of fibrinogen degradation products (FDPs), increased concentrations of which interfere with fibrin polymerization and platelet aggregation, thus attenuating the effects of increases in thrombin activity. In fact, higher FDP levels are seen in patients receiving streptokinase than in those administered t-PA, resulting in prolonged anticoagulant activity in streptokinase-treated patients.

Although the specific mechanisms for activation of the coagulation system by plasmin are not yet defined, it appears that inhibition of thrombin with heparin-antithrombin III or hirudin is effective in limiting significant fibrin formation. These results emphasize the need for concomitant administration of an anticoagulant when plasminogen activation is induced with fibrinolytic agents. Further characterization of the mechanisms responsible for activation of the coagulation system by plasmin should allow for development of specific strategies to inhibit its occurrence.

PROCOAGULANT ACTIVITY OF THE THROMBUS

Increased procoagulant activity associated with the coronary thrombus is probably the most important determinant of the rate of clot lysis and the occurrence of rethrombosis. Thrombin binds to fibrin in the thrombus and remains active, resulting in continued formation of fibrin.[7,8,36–38] During clot lysis, active thrombin may be released or exposed on the thrombus surface.[8] Thrombin bound to fibrin appears to be relatively protected from inhibition by heparin-antithrombin III, and thus conventional adjunctive heparin therapy would be expected to be relatively ineffective in inhibiting thrombin activity associated with the thrombus.[39] In addition to inducing fibrin formation, thrombin activity associated with the thrombus may activate platelets, causing platelet aggregation and vascular occlusion.[21]

During the initial stage of thrombosis, factor XIIIa not only induces cross-linking of fibrin, which stabilizes the fibrin mesh, but also cross-links α_2-antiplasmin to fibrin. The α_2-antiplasmin bound to fibrin in the thrombus appears to attenuate significantly the rate of clot lysis, judging from the accelerated lysis that occurs when a monoclonal antibody that inhibits α_2-antiplasmin is administered with t-PA.[13]

A high concentration of platelets in coronary thrombi appears to attenuate the rate of clot lysis induced by fibrinolytic agents, compared with the rate in platelet-poor thrombi. Although the mechanisms are not known, release of plasminogen activator inhibitor-1 by platelets may account for decreased lytic efficiency with t-PA.[40]

COMPARISON OF NEW THROMBIN INHIBITORS AND THEIR ROLE AS ADJUNCTIVE AGENTS

Elaboration of thrombin appears to be the critical determinant in the formation of a thrombus. Thrombin can activate cofactors V and VIII to increase activation of prothrombin, convert fibrinogen to fibrin, activate factor XIII to stabilize the forming fibrin mesh, and activate platelets. Recently, several experimental studies showed that new thrombin inhibitors with mechanisms of action that are antithrombin III-independent are more effective than heparin in preventing platelet-rich arterial thrombosis[5,41] and in inhibiting reocclusion after thrombolytic therapy.[21-23] The potency of these new thrombin inhibitors may be attributable to their greater inhibitory activity toward thrombin bound to fibrin, compared with heparin-antithrombin III.

Thrombin binds to fibrin at 2 distinct sites, 1 near the active site and the other referred to as the anion exosite.[42] The anion exosite also appears to be involved in thrombin binding to heparin, heparin fractions, hirudin, thrombomodulin (Fig. 3), and platelet receptors.[43] Potent thrombin inhibition can be achieved by inhibition of anion exosite-mediated binding with fragments of hirudin, a small peptide isolated from leech salivary glands,[44,45] and other peptides recognized by thrombin.[46] In addition to binding to the anion exosite, hirudin binds to the thrombin-active site, inducing irreversible inhibition. Potent antithrombin III-independent inhibition of thrombin activity has also been achieved with small synthetic peptide inhibitors that bind to the thrombin-active site.[47,48] Presumably, such inhibitors would have access to the active site even when thrombin is bound to fibrin. Several of these antithrombin III-independent inhibitors have been developed for clinical use and appear to have the potential to prevent arterial thrombosis, accelerate clot lysis induced by fibrinolytic agents, and prevent rethrombosis after thrombolytic therapy.

Weitz et al[7] found in an in vitro clot lysis system that heparin-antithrombin III was relatively inefficient at inhibiting thrombin activity associated with clot. Hirudin was more effective than heparin-antithrombin III in inhibiting clot-associated thrombin activity, but hirugen (which inhibits only anion exosite-dependent binding) was more effecive than hirudin. Similarly, d-phe-pro-arg chloromethyl ketone (PPACK), a small peptide inhibitor of the thrombin-active site, was equally effective in inhibiting clot-associated thrombin activity and thrombin activity in solution. Hirugen and other peptides derived from the region of hirudin that interact with the anion exosite have been found in other in vitro studies to be more potent inhibitors than hirudin.[44-46] Nonetheless, hirudin is a potent antithrombin in vivo and has been shown to inhibit platelet-rich arterial thrombosis in response to vessel wall injury.[22] Heparin in the same model was relatively ineffective, even at very high concentrations. Hirudin has also been shown in an experimental canine preparation to prevent rethrombosis after thrombolysis, and because of these encouraging preliminary results, there is considerable interest in a clinical trial of recombinant hirudin. Whether derivatives of this agent will be more effective than the parent molecule remains to be established, but based on in vitro results, inhibition of the anion exosite appears to be a particularly effective strategy for inhibiting thrombin.

Several small synthetic inhibitors of thrombin have been developed. Argatroban, one of these inhibitors, appears to be particularly promising based on results of preliminary studies. In canine preparations, this drug accelerated the time to clot lysis and prevented coronary reocclusion in a preparation of coronary thrombolysis with residual high-grade stenosis.[21,23] Whether these agents will have advantages over hirudin remains to be established.

CONCLUSIONS

Multiple mechanisms appear to contribute to increased procoagulant activity during thrombolysis and will need to be defined more extensively. However, it is apparent that the consequences of increased procoagulant activity are delay or failure of clot lysis and recurrent thrombosis. Although heparin is effective in limiting some of the procoagulant activity that occurs, more effective strategies are emerging. Preliminary results suggest that more potent thrombin inhibition or inhibition of factors that initiate thrombosis as adjunctive therapies during thrombolysis may be more effective than heparin alone.

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Adjunctive Use of Beta-Adrenergic Blockers, Calcium Antagonists and Other Therapies in Coronary Thrombolysis

Richard C. Becker, MD, and Joel M. Gore, MD

The availability of thrombolytic agents for use in the treatment of acute myocardial infarction is an important step in the management of a common, often debilitating, and potentially lethal disorder. However, despite the proven benefits of coronary thrombolysis, the importance of adjunctive treatment modalities is being increasingly recognized. β-adrenergic blockers, calcium antagonists, nitrates, magnesium, and angiotensin-converting enzyme inhibitors each exert favorable cardiovascular properties that may offer additional benefits. Clinical trials combining thrombolytic and adjunctive pharmacologic agents offer hope for further advances in the treatment of acute myocardial infarction.

(Am J Cardiol 1991;67:25A–31A)

Thrombolytic therapy has revolutionized the treatment of acute myocardial infarction (MI), reducing infarct size, preserving ventricular function, and improving patient survival. However, MI remains a leading cause of morbidity and mortality, and is responsible for >600,000 deaths in the United States annually. Moreover, patients surviving an MI remain at substantial risk for reinfarction and sudden cardiac death. Clearly, despite the benefits of thrombolytic therapy, the use of adjuvant therapies, including β-adrenergic blockers, magnesium, nitrate preparations, calcium antagonists, and angiotensin-converting enzyme (ACE) inhibitors must be explored.

BETA-ADRENERGIC BLOCKERS

Beta blockers reduce myocardial oxygen demand through a reduction in heart rate, systemic blood pressure and myocardial contractility. In addition, they counter the excessive production of catecholamines frequently seen in acute MI. Given these favorable properties, β blockers have been extensively investigated in the setting of acute MI.[1]

When given intravenously during the early stages of infarction (<12 hours from symptom onset), β blockers have been shown to reduce both infarct size and the incidence of complex ventricular arrhythmias. The impact of β-blocker therapy on in-hospital mortality, reinfarction and cardiac arrest has been examined in a total of 27 randomized trials involving more than 27,000 patients.[1] Overall, patients treated with β blockers experienced a 13% reduction in mortality; the survival advantage was most evident during the first 2 postinfarct days. Patients treated with β blockers also had a reduction in nonfatal reinfarction and cardiac arrest of 19 and 16%, respectively.

The decreased mortality rate during the initial 48-hour postinfarction phase may, at least in part, translate into a reduction in myocardial rupture. If this is indeed the case, β blockers may have an additional role in patients receiving thrombolytic therapy in whom the incidence of myocardial rupture may be increased when treatment is initiated relatively late (>12 hours) after symptom onset.[2]

In the recently completed Second Thrombolysis in Myocardial Infarction (TIMI-2) trial,[3] a subgroup of 1,390 patients were randomly assigned to immediate intravenous metoprolol followed by oral metoprolol, or oral metoprolol begun on postinfarct day 6. Patients receiving β blockers, calcium antagonists or those with contraindications at the time of study entry were not considered

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eligible. Whereas in-hospital and 42-day mortality rates were similar in both treatment groups, patients randomized to immediate intravenous β blockade experienced significantly fewer recurrent ischemic events and nonfatal reinfarctions. Furthermore, patients treated within 2 hours of symptom onset and those in a low-risk subgroup derived the greatest overall benefits, experiencing significant reductions in cardiac events (death, recurrent infarction) at 42 days.

In TIMI-2B, a trend toward less frequent intracranial hemorrhages was observed in patients assigned to immediate β-blocker therapy. Of particular interest, intracranial hemorrhagic events were not observed among 631 patients treated with intravenous metoprolol and 100 mg of tissue-type plasminogen activator (t-PA) (Gore et al, unpublished observations). A critical examination of the available data supports the adjuvant use of β blockers in the treatment of patients with MI receiving thrombolytic therapy.

MAGNESIUM

In recent years, considerable attention has been paid to the role of magnesium (Mg^{2+}) in cardiovascular disease.[4-7] Magnesium plays an essential role in maintaining cellular membrane potential at rest. Mg^{2+} deficiency is associated with: (1) a reduction in intracellular potassium; (2) an increase of intracellular sodium; and (3) augmentation of cell excitability. In patients with acute MI, several studies reported a transient decrease in serum Mg^{2+} levels, resulting from adrenergic stimulation and increased aldosterone secretion.

Dyckner[8] observed a 46% incidence of hypomagnesemia among 342 patients with acute MI. In addition, patients with hypomagnesemia were found to be at increased risk for ventricular arrhythmias. Three placebo-controlled, double-blinded studies examined the effects of magnesium administration in patients with known or suspected acute MI.[9-11] In each study, Mg^{2+} administration was associated with a 50% reduction in ventricular arrhythmias. In one study,[11] early Mg^{2+} administration (within the initial 24 hours of suspected acute MI) was associated with a significant reduction in 1-year mortality. The mechanisms underlying magnesium's beneficial effects in acute MI are likely multiple, including antiarrhythmic, antispasmodic and antithrombotic properties.

The antithrombotic properties of Mg^{2+} were investigated in a number of experimental animal models. Decreased platelet adhesion and aggregation were demonstrated in injured or stenosed canine arterial segments pretreated with Mg^{2+}. In addition, repeated intravenous infusions of isotonic $MgCl_2$ were shown to decrease local thrombus formation and prevent distal arterial embolization.[12,13] Vascular spasm can be prevented with Mg^{2+}, thereby limiting platelet-mediated vasoconstriction.[13]

In patients with acute MI, hypomagnesemia is associated with increased platelet aggregability.[14] Therefore, it could conceivably play a role in thrombolytic resistance and coronary arterial reocclusion. Moreover, a transient state of Mg^{2+} deficiency could also limit microvascular blood flow, increasing infarct size and adversely affecting myocardial function.[15,16]

Routine determination of Mg^{2+} levels should be performed in patients with a high likelihood of hypomagnesemia, including those with congestive heart failure or systemic hypertension who are receiving diuretic therapy. Magnesium supplementation should be given as indicated. It must be appreciated, however, that even in the presence of normal serum Mg^{2+} levels, many patients may have low intracellular levels. Therefore, in patients with either torsades de pointes ventricular tachycardia or complicated MI, Mg^{2+} administration may be beneficial regardless of the serum Mg^{2+} level.

The potential importance and clinical relevance of Mg^{2+} deficiency in MI dictates that further evaluation be undertaken. At this time, it appears that ISIS-4 (Fourth International Study of Infarct Survival) will explore this area.

NITRATE PREPARATIONS

Intravenous nitroglycerin, when used in the setting of an evolving acute MI, has been shown to limit infarct size, prevent infarct expansion, and decrease both morbidity and mortality. These benefits are most likely related to an improvement in the balance between myocardial oxygen supply and demand. The use of intravenous nitrates has not been independently assessed, however, in clinical trials of thrombolytic therapy.

A recent study by Jugdutt and Warnica[17] found that intravenous nitroglycerin reduced infarct size in both anterior and inferior locations. The benefit was greatest in patients given therapy within 4 hours of onset of symptoms and in those in whom a mean systemic blood pressure of 80 mm Hg was maintained. An improvement in left ventricular ejection fraction and hemodynamic parameters was also observed. Moreover, nitroglycerin reduced the frequency of infarct-related complications, including infarct expansion and extension, cardiogenic shock, cardiac death and left ventricular thrombus formation. In the setting of coronary thrombolysis, the favorable hemodynamic properties of nitrolgycerin, coupled with its ability to reduce myocardial ischemia, may be of particular importance. Conceptually, nitroglycerin may initiate a series of protective effects that could subsequently be maintained with the addition of an ACE inhibitor in the early postinfarction phase.

In MI, nitrate tolerance develops progressively during prolonged intravenous infusions. At low doses, however, tolerance is only partial and does not compromise the beneficial effects of therapy.[17]

Previous in vitro and in vivo studies showed that nitroglycerin has platelet-inhibiting properties.[18,19] However, the antiplatelet effects were inconsistently observed and frequently were produced only with extremely high concentrations of nitroglycerin. A recent clinical study[20] performed in patients with acute ischemic syndromes did demonstrate, however, that nitroglycerin given in standard doses decreases adenosine diphosphate and thrombin-mediated platelet aggregation. Of interest and clinical relevance, the antiplatelet effects were quickly reversed with discontinuation of the nitroglycerin infusion.

The mechanism(s) underlying nitroglycerin's antiplatelet properties have not been fully defined. Although some evidence supporting an increase in prostacyclin generation exists,[21] current evidence suggests that nitroglycerin may stimulate guanylate cyclase, resulting in an increase in cyclic guanosine monophosphate.[22] Although limited investigation has taken place, nitroglycerin's antiplatelet properties may be of importance in promoting successful coronary thrombolysis and preventing reocclusion.[23] They may also aid in the maintenance of microvascular blood flow after coronary reperfusion.

Intravenous heparin is a frequently used adjunct with intravenous nitroglycerin. Patients receiving intravenous infusions of both agents often require a larger heparin dose to achieve and maintain a therapeutic state of systemic anticoagulation than patients receiving intravenous heparin alone. In a study performed at our institution,[24] patients receiving intravenous nitroglycerin at relatively low infusion rates did not manifest heparin resistance. However, patients given high infusion rates (>350 μg/min) required increased amounts of heparin to maintain a therapeutic state of systemic anticoagulation. Moreover, antithrombin III activity was significantly decreased and correlated directly with the intravenous nitroglycerin dose. In clinical practice, it is possible that nitroglycerin-induced heparin resistance may compromise overall treatment response. This may be of particular importance in coronary thrombolysis, where adequate heparinization is of critical importance, preventing coronary reocclusion and left ventricular mural thrombus formation.[25,26] In addition, intravenous nitroglycerin-induced heparin resistance could increase the risk of hemorrhagic complications associated with systemic anticoagulation. Theoretically, after a reduction in intravenous nitroglycerin dose to <350 μg/min, its inhibitory effects may lessen substantially (reduced heparin resistance), causing a state of excessive systemic anticoagulation.

Intravenous nitroglycerin is a highly effective agent in patients with acute MI. Its coronary vasodilating, preload reducing and antiplatelet effects justify nitroglycerin's routine use during the initial 24 to 48 hours after the administration of thrombolytic therapy.

CALCIUM ANTAGONISTS

The mechanism of cellular injury during ischemia and reperfusion is an area of great interest and clinical importance. Despite a paucity of direct evidence, calcium appears in a prominent position in most hypothetical schemes that link the interruption and restoration of blood flow to histologic and functional abnormalities within the myocardium.[27,28] A sudden rise of intracellular calcium (1) depletes high-energy phosphate stores; (2) decreases oxidative phosphorylation; (3) activates enzymes capable of damaging cell membranes and cytoskeletal proteins; (4) alters the functional capabilities of cellular proteins; and (5) increases arrhythmias mediated by delayed after-depolarizations (Table I).[29-31]

TABLE I Physiological Effects of Intracellular Calcium Accumulation

- Depletion of high-energy phosphate stores
- Decreased oxidative phosphorylation
- Activation of cytotoxic enzymes
- Altered cellular protein function
- Increased substrate for ventricular "late potentials"

To date, 22 clinical trials have examined the effects of calcium antagonists (nifedipine, verapamil, diltiazem) on clinical outcome among patients with either a threatened or confirmed MI.[32-56] Overall, beneficial effects on infarct size, left ventricular function, progression to infarction, recurrent angina, rate of reinfarction and mortality have not been observed. In fact, a number of trials identified an unfavorable outcome among patients treated with the calcium antagonist nifedipine.[32,36-39]

The Diltiazem Reinfarction Study[52,53] is the only clinical trial that addressed the specific issue of non-Q-wave MI. Overall, 567 patients were randomly treated with either diltiazem (90 mg every 6 hours) or placebo between 24 and 72 hours after the onset of infarction. At 14 days, patients receiving diltiazem were found to have a significantly lower incidence of recurrent infarction, postinfarction angina, and angina associated with ST-T-wave changes than patients given placebo.

The Multicenter Diltiazem Postinfarction Trial,[57] while not designed specifically to investigate patients with non-Q-wave infarctions, did include 634 such patients.[56] The cumulative incidence of cardiac death and nonfatal reinfarction at 1 year was 15% in the placebo group versus 9% in the diltiazem group, a reduction of 40%. This beneficial effect was maintained for >4 years. Therefore, diltiazem has been recommended for patients sustaining a non-Q-wave MI in whom left ventricular function is preserved.[57-59]

The beneficial effects observed in short- and long-term trials with the calcium antagonist diltiazem, coupled with the histologic and anatomic similarities between spontaneous and pharmacologically induced reperfusion in MI, suggest that it may serve as an important adjuvant after coronary thrombolysis.[60,61] Despite theoretical and clinical support, however, randomized trials of diltiazem in combination with a thrombolytic agent have not been performed. In contrast, an isolated study including 149 patients with MI receiving thrombolytic therapy in combination with nifedipine failed to identify a significant improvement in global left ventricular function, regional wall motion, infarct size or early mortality.[62]

The mechanism(s) underlying the beneficial effects of diltiazem in patients with non-Q-wave MI are being intensely investigated. Beyond the ability of diltiazem (and other calcium antagonists) to reduce systemic blood pressure, dilate coronary arteries, improve myocardial blood flow and reduce ventricular wall stress, the capacity to prevent reinfarction suggests that it may possess antithrombotic properties as well. Indeed, calcium ions and cyclic nucleotides are interrelated factors in the coupling

TABLE II Physiological Effects of Angiotensin-Converting Enzyme Inhibitors on the Coronary Vasculature

- Increased coronary blood flow
- Decreased cellular proliferation
- Decreased inflammatory response to local injury
- Decreased edema formation

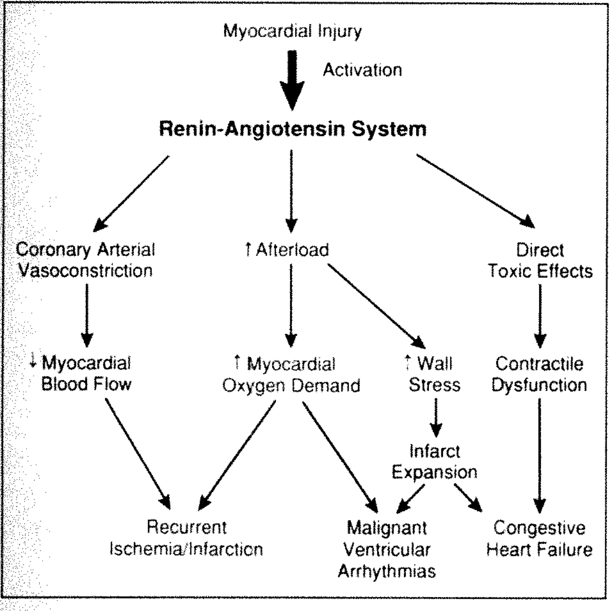

FIGURE 1. Myocardial injury activates the renin-angiotensin system, which in turn exerts a number of unfavorable properties on the myocardium, peripheral vasculature and coronary arteries.

of extracellular messages to intracellular responses, such as platelet activation. Calcium antagonists have been shown to decrease platelet nucleotide release, thromboxane A_2 generation and aggregation in response to adenosine diphosphate, collagen and epinephrine.[63] Diltiazem appears to have the greatest overall antiplatelet properties[64] and, in addition, its effects are enhanced in the presence of β-adrenergic blockers[65] and low-dose aspirin.[66] Moreover, diltiazem has been shown to inhibit platelet activating factor[67] and increase vascular endothelial prostacyclin release.[68]

Overall, the antiplatelet properties of calcium antagonists may reduce thrombotic tendency; however, they may impair systemic hemostasis as well.[69,70] In the combined TIMI-2 pilot and randomized clinical trial, 3,924 patients with MI were treated with t-PA, heparin and aspirin. Adverse neurological events occurred in 56 patients, 23 of whom had an intracerebral hemorrhage. Of interest and clinical importance, patients receiving calcium antagonists at the time of their MI had a fourfold increased risk of an intracranial hemorrhage. This risk persisted after controlling for t-PA dose and other potential risk factors (Gore et al, unpublished observations).

The available evidence suggests that the combined administration of calcium antagonists and thrombolytic agents warrants further investigation.

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

Specific genes coding for renin and angiotensin are expressed in all regions of the heart, including the epicardial coronary arteries and resistance arterioles. Functional and physiologically active pathways required for the conversion of angiotensin I to angiotensin II are also present.[71] Locally generated vascular angiotensin is intimately involved in the regulation of coronary blood flow, and it also participates in the vascular response to injury by stimulating cellular proliferation, inflammation and edema formation (Table II).[72-74]

Angiotensin-converting enzyme inhibitors antagonize the renin-angiotensin system locally by preventing the synthesis of vascular angiotensin II, a potent vasoconstrictor, and by facilitating the generation of vasoactive mediators such as bradykinin, prostacyclin and endothelium-derived relaxing factor.[75,76]

With MI, the onset of myocardial injury triggers a sudden and profound increase in activity within the sympathetic and renin-angiotensin systems. It has been demonstrated that patient outcome may, in fact, be predicted by the intensity of the neurohumoral response to myocardial injury.[77,78] By increasing myocardial oxygen demands and enhancing coronary arterial vasoconstriction, neurohumoral activation can promote infarct expansion, recurrent ischemia, reinfarction, congestive heart failure and malignant arrhythmias.[79] In addition, angiotensin II may possess toxic properties similar to those of norepinephrine, which can directly and adversely affect the myocardium (Fig. 1).[80]

Beta-adrenergic blocking agents have been shown to improve patient outcome after MI. These beneficial effects may indeed be the direct result of their ability to attenuate heightened sympathetic tone in the peri-infarction and postinfarction phases.[3] In experimental models, ACE inhibitors have been shown to decrease infarct size and enhance myocardial performance.[81,82] In addition, patients receiving ACE inhibitors after MI are less likely to develop either infarct expansion[83,84] or experience high-grade ventricular arrhythmias.[85] Experience with coronary occlusion-reperfusion models in animals demonstrated that anatomic and metabolic abnormalities within the microvasculature, including capillary disruption, endothelial swelling, intraluminal protrusions, myocyte swelling with capillary impingement, mitochondrial calcium accumulation, and leukocyte plugging, occur at the moment of reperfusion.[86-89] Human autopsy studies after coronary thrombolysis identified areas of contraction band necrosis (a reperfusion-mediated phenomenon) within the infarct zone,[90] and although contraction band necrosis may represent irreversibly damaged myocytes, recent evidence suggests that these areas may indeed be salvageable.[91]

The mechanism underlying reperfusion injury is not reperfusion itself but reoxygenation.[92] Consequently, the contribution of oxygen-derived free radical injury during reperfusion has become a major area of concern in patients receiving thrombolytic therapy. Oxygen radicals are capable of reversibly or irreversibly damaging compounds of all biologic classes, including nucleic acids, proteins, lipids, carbohydrates and connective tissue macromolecules. Oxygen radicals may also adversely influence membrane function, cellular metabolism and gene expression.[93]

Under experimental conditions, ACE inhibitors have been shown to improve ventricular contractile dysfunction and reduce malignant ventricular arrhythmias after reperfusion. While the mechanisms are multifactorial, including (1) increased myocardial blood flow, (2) preservation of intracellular high-energy phosphates, and (3) attenuation of the renin-angiotensin system,[94–97] the ability of ACE inhibitors to act as free-radical scavengers remains controversial. Recent evidence suggests, however, that ACE inhibitors do not directly scavenge free radicals, but act indirectly as antioxidants, or by altering the intracellular concentration of cytochrome C.[98]

Thrombolytic therapy is designed to establish vessel patency and restore blood flow to a threatened myocardium. Despite recent evidence that the renin-angiotensin system is activated locally by vascular injury, t-PA, and plasmin,[99,100] and experimental and clinical evidence suggesting a role for ACE inhibitors in the prevention of reperfusion injury, infarct expansion, and malignant arrhythmias, trials investigating combined thrombolytic and ACE inhibitor therapy have been scarce. Preliminary results from a recently completed pilot study[101] suggest, however, that large-scale clinical trials are indeed warranted. It is anticipated that ISIS-4 will explore this area of investigation.

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Summary

Robert Roberts, MD

Data from the Heparin-Aspirin Reperfusion Trial, Bleich and Sixth European Cooperative Study Group trials confirmed the benefits of early intravenous heparin as an adjunct to thrombolytic therapy with tissue plasminogen activator (t-PA). The second Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI-2) suggested that streptokinase and t-PA were equally effective in reducing mortality associated with acute myocardial infarction; however, critics noted that the heparin regimen used in GISSI-2 was delivered subcutaneously and was therefore suboptimal in conjunction with t-PA. Investigators concluded that the need for heparin administered early and in high doses is greater in patients treated with t-PA than in those treated with streptokinase, because t-PA has less systemic anticoagulant effects than does streptokinase.

Results of 2 large international trials will be forthcoming and hopefully will shed more light on the role of adjunctive agents in thrombolysis. The third International Study of Infarct Survival (ISIS-3) will compare duteplase (a Burroughs Wellcome t-PA formulation), streptokinase and anisoylated plasminogen activator complex in >30,000 patients. However, in this trial, the heparin regimen is also suboptimal for use with t-PA, because heparin will be administered subcutaneously 4 hours after initiation of therapy. Also, the t-PA that will be used in ISIS-3 appears to be underdosed, compared to the alteplase regimen currently used in the United States. Recent reports suggest that duteplase will not be marketed in the United States. Thus, ISIS-3 will not be a true comparison of the 3 agents. Such a comparison would necessitate use of early intravenous heparin with adequate dosing in the t-PA arm.

In response to questions raised by GISSI-2, a new trial is planned to evaluate t-PA and streptokinase with an appropriate heparin regimen. The Global Utilization of Streptokinase and t-PA for Occluded Arteries (GUSTO) trial will be conducted outside the United States and will include >30,000 patients. At present, the protocol is planned to include 3 arms: a rapid infusion dose of up to 100 mg of t-PA administered over 90 minutes; a standard dose of 1.5 million U streptokinase administered over 60 minutes; and a combination arm of 1 mg/kg (maximum, 90 mg) t-PA administered over 60 minutes (with 10% as a bolus), plus 1 million U streptokinase over 60 minutes. The rationale for the combined arm is to use t-PA to open the artery, and then streptokinase as a "super heparin" to maintain patency over the first 24 hours. The primary end point will be mortality at 30 days. GUSTO should begin enrolling patients shortly.

Overall, the studies to date suggest that heparin and aspirin are important adjuncts to thrombolytic therapy, and that newer adjunctive strategies will be useful in shortening the time to thrombolysis and maintaining patency by preventing reocclusion/rethrombosis.

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The American Journal of Cardiology®

APRIL 22, 1991

A Symposium: Position of Beta Blockers in Present and Future Therapy of Systemic Hypertension

GUEST EDITORS:

Kikuo Arakawa, MD
Department of Internal Medicine II
School of Medicine
Fukuoka University
Fukuoka, Japan

Pieter A. van Zwieten, MD, PhD
University of Amsterdam
Amsterdam, The Netherlands

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The American Journal of Cardiology®

APRIL 22, 1991 VOL. 67 NO. 10

A SYMPOSIUM:
POSITION OF BETA BLOCKERS IN PRESENT AND FUTURE THERAPY OF SYSTEMIC HYPERTENSION

1B
Introduction
Kikuo Arakawa

3B
Autonomic Nervous System Dysregulation in Human Hypertension
Stevo Julius

8B
Pharmacologic Characterization of Beta Blockers With Special Reference to the Significance of Nonspecific Membrane Effects
Shoichi Imai

13B
Vasodilation, Not Cardiodepression, Underlies the Antihypertensive Effect of Beta-Adrenoceptor Antagonists
Arie J. Man In't Veld

18B
Blood Pressure During Sleep: Antihypertensive Medication
Osamu Tochikubo, Kosuke Minamisawa, Tomomi Miyakawa,
Eiji Miyajima, Yoshito Fujiki, and Masao Ishii

26B
Antihypertensive Agents, Serum Lipoproteins and Glucose Metabolism
Paolo Ferrari, Johan Rosman, and Peter Weidmann

36B
Bopindolol: Czechoslovak Experience With a New Beta Blocker in the Treatment of Hypertension
Jiří Widimský, Kateřina Lefflerová, Ivo Dvořák, Věra Fedelešová,
Zdeněk Lupínek, Otto Mayer, and Eliška Pinterová

43B
Review of State-of-the-Art Beta-Blocker Therapy
Lennart Hansson

47B
Clinical Experience With Bopindolol: Summary of Poster Presentations
Masaharu Ikeda and Yoshiyuki Nakashima

The American Journal of Cardiology

Introduction

Kikuo Arakawa, MD

The role of the sympathetic nervous system (SNS) in the etiology of essential hypertension was controversial until 1 to 2 decades ago. It has now been clarified at least to some extent. Doctor Julius has shown some evidence that strongly suggests that the SNS may play a role in young borderline hypertensive individuals whose hemodynamics are characterized by increased heart rate, cardiac output and plasma norepinephrine levels. He attributes these abnormalities to alterations in the higher integrative centers in the medulla oblongata. As hypertension becomes established, however, heart rate and cardiac output decrease and sympathetic tone seems to decrease, even though high blood pressure is still maintained by increased vascular resistance. In this connection, he proposes the interesting concept of the "blood pressure-seeking property of the central nervous system [CNS]," implying that one may most properly control blood pressure by intervening at the level of the CNS.

One way of blocking the effect of the SNS on the circulation is with an antagonist at the β-adrenoceptor level. This was discovered nearly 30 years ago by Doctor Black, for which he received a Nobel Prize in 1988. Ever since, many types of β blockers with different properties have been developed. Of these, hydrophilicity, with or without intrinsic sympathomimetic activity (ISA) and/or membrane stabilizing activity, duration of action, presence or absence of vasodilation, etc., are reviewed by Doctor Imai.

Use of a β blocker was first applied to the treatment of angina because it blocked adrenergically driven cardiac work. It was found by Dr. Prichard, in 1965, that β blockers produce an accompanying reduction of blood pressure, which opened the way for their application to the pharmacotherapy of hypertension. As Doctor Man in't Veld points out, this action of the β blockers was thought to be due to a decrease in cardiac output, but not in vascular resistance. However, as he demonstrates, all β blockers eventually reduce vascular resistance.

Doctor Tochikubo warns that blood pressure should not be reduced too much at night, since elderly hypertensive patients have especially low cardiac output at night and their blood pressure is regulated mainly by vascular resistance. Therefore, he cautions against the use of direct vasodilative drugs in elderly hypertensive patients, and believes that β blockers are preferable.

The final goal of antihypertensive therapy is to prevent cardiovascular accidents. However, despite great expectations, several large-scale clinical trials have failed to demonstrate that β blockers, together with diuretics, are able to prevent coronary artery disease. Of many possible reasons for this, adverse effects on other risk factors, such as lipid and glucose metabolism, have been suggested, as reviewed by Doctor Weidmann. According to his analysis, diuretics and β blockers without ISA seem to be the worst in this respect, whereas β blockers with ISA are better and α blockers are the best. Calcium antagonists and angiotensin-converting enzyme (ACE) inhibitors seem to be neutral in terms of lipid and glucose metabolism.

Doctor Widimsky et al discuss their experience in Czechoslovakia with bopindolol, a long-acting (once-a-day administration) β blocker with ISA. In both open and double-blind studies, they have reported excellent efficacy for bopindolol, including improvement in the atherosclerotic index, in apolipoprotein A/apolipoprotein B and in platelet aggregation, without serious adverse reactions and without any deterioration in glucose metabolism.

Finally, Doctor Hansson has reviewed all β blockers and concluded that in several respects β blockers appear to hold promise for the future treatment of hypertension.

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In my view, older drugs such as diuretics and β blockers seem to have lost their premier position in recent years because of the superiority of newer drugs such as calcium antagonists and ACE inhibitors, especially with regard to their effects on lipid and glucose metabolism.

In this supplement, however, we learn that sympathetic mechanisms are involved in the etiology of essential hypertension. Therefore antagonists of this system—such as β blockers, especially improved β blockers such as bopindolol—remain essential not only in theory, i.e., because of their efficacy and tolerability, but also for their effects on lipid and glucose metabolism, quality of life and duration of therapeutic effect. Cardioprotective effects, therefore, can still be expected in theory. Meanwhile, we must wait for clinical confirmation of a primary cardioprotective effect.

Autonomic Nervous System Dysregulation in Human Hypertension

Stevo Julius, MD, DSc

An increased sympathetic drive combined with decreased parasympathetic inhibition is found in patients with borderline hypertension, who characteristically have rapid heart rates, high cardiac output and relatively normal vascular resistance (hyperkinetic state). In established hypertension, cardiac output is normal, vascular resistance is elevated and signs of increased sympathetic drive are absent. Apparently hemodynamics and sympathetic drive change during hypertension. The mechanism of the hemodynamic transition in the course of hypertension is well understood. Cardiac output returns from elevated to normal values as β-adrenergic receptors down-regulate and stroke volume decreases (due to decreased cardiac compliance). The high blood pressure induces vascular hypertrophy, which in turn leads to increased vascular resistance. The mechanism of the change of sympathetic tone from elevated in borderline hypertension to apparently normal in established hypertension can best be explained within the conceptual framework of the "blood-pressure-seeking" properties of the brain. In hypertension, the central nervous system seeks to maintain systemic blood pressure at the higher level. As hypertension advances and vascular hypertrophy develops, arterioles become hyperresponsive to vasoconstriction. At this point, less sympathetic drive is needed to maintain pressure-elevating vasoconstriction, and the central sympathetic drive is down-regulated. The etiology of increased sympathetic drive in hypertension remains unresolved. Subjects with increased sympathetic drive are also usually overweight and have elevated levels of insulin, cholesterol and triglycerides, as well as decreased high-density lipoproteins. Future research must focus on the link between coronary risk factors and sympathetic overactivity in hypertension.

(Am J Cardiol 1991;67:3B–7B)

At first glance, studies of the role of the autonomic nervous system (ANS) in human hypertension yield somewhat controversial results. An abnormality is easily demonstrated in young patients with borderline hypertension, but when older patients with established hypertension are studied, there is very little evidence for ANS dysregulation. This raises a number of questions: are young subjects with borderline hypertension a separate subgroup who either do not develop established hypertension, or, if they develop established hypertension, is the condition so rare that it cannot be distinguished from the larger pool of subjects who have a non-neurogenic established hypertension? If subjects with neurogenic borderline hypertension later develop established hypertension, why is it so difficult to show an autonomic abnormality in established hypertension? Does this mean that the ANS initiates hypertension but later does not play a role in its maintenance? What is the mechanism of transition from an apparently neurogenic to a seemingly non-neurogenic form of hypertension?

The purpose of this article is to review the evidence about the role of the ANS in hypertension and to provide answers to some of the questions.

AUTONOMIC ABNORMALITY IN BORDERLINE HYPERTENSION

The stimulus to study the role of the ANS in borderline hypertension comes from observation of the characteristic "hyperkinetic" hemodynamics, consisting of a high cardiac output, fast heart rate and increased stroke volume.[1-5] Brod[6] suggested that this picture resembles the hemodynamic state during emotional excitement—the so-called "fight or flight" reaction. Whether the hemodynamic pattern in borderline hypertension is indeed due to an emotional response remains unresolved. However, it has been shown without a doubt that an autonomic dysregulation is the basic mechanism in borderline hypertension, because cardiac "denervation" by auto-

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nomic blockade abolishes the increase of cardiac output that occurs in this state.[7]

An increased sympathetic tone in borderline hypertension has been documented by different experimental methods. An increased rate of bursts of activity in the sympathetic fibers of the peroneal nerves has been demonstrated with direct microneurographic recordings in cases of borderline hypertension.[8] Plasma norepinephrine levels in such patients are elevated.[9] Studies with radioisotope tracers found increased norepinephrine spillover rates in young subjects with mild hypertension.[10] Sympathetic tone can also be assessed by spectral analysis of the electrocardiogram, and increased sympathetic activity in mild hypertension has been found by that method.[11]

Increased sympathetic tone in borderline hypertension is coupled with a decrease in parasympathetic activity. Intravenous atropine elicits a smaller increase of heart rate and cardiac output in borderline hypertension, suggesting that, compared with normotensive subjects, borderline hypertensive subjects have less cardiac parasympathetic inhibition.[7] Spectral analysis of the heart rate yields a similar picture of decreased parasympathetic tone in mild hypertension.[11] Decreased parasympathetic tone is evident also in noncardiovascular regions. In studies of patients with borderline hypertension, Bohm et al[12] found a significant reduction of the parasympathetically mediated salivary flow rates.

Since the reciprocal coupling of the sympathetic and parasympathetic tone characteristically occurs at the level of cardiovascular centers in the medulla oblongata, the inverse relationship of sympathetic and parasympathetic tone in borderline hypertension suggests that the autonomic abnormality is of central nervous system (CNS) origin. As one would expect with central derangement, the autonomic abnormality in borderline hypertension is widespread. Alpha-adrenergic drive to the arterioles is increased,[13] particularly in borderline hypertensives, who also have higher plasma renin activity. We speculated that this high renin may reflect an enhanced renal β-adrenergic drive in borderline hypertension.[14] This notion has been confirmed by Esler et al,[15] who found a substantial enhancement of the regional renal spillover of norepinephrine in borderline hypertension. Two other abnormalities, decreased plasma volume[16] and increased venous tone[17,18] in borderline hypertension, can also be explained by an increased sympathetic tone.

EVIDENCE THAT NEUROGENIC BORDERLINE HYPERTENSION LEADS TO ESTABLISHED HYPERTENSION

Subjects with borderline hypertension are at a higher risk of developing more severe forms of hypertension, but that risk is not overwhelming. Over the course of 20 years it is likely that about 70% of young subjects with borderline hypertension will not progress to permanent, established hypertension.[19] Therefore, it is important to determine the prognosis specifically for subjects with neurogenic borderline hypertension. In clinical practice there is good evidence that the hyperkinetic state, which is demonstrably associated with increased sympathetic stimulation and decreased vagal inhibition of the sinus node, is a precursor of future hypertension. A fast heart rate in youth is a predictor of future hypertension.[20-22] Longitudinal studies also indicate that the underlying hemodynamics evolve from a hyperkinetic state of high cardiac output into a state of increased vascular resistance.[23,24] This evolution from hyperkinetic-borderline hypertension to increased-vascular-resistance clinical hypertension requiring treatment has been demonstrated by Lund-Johansen and Omvik.[25] In a unique study, these investigators followed and repeatedly studied a group of subjects with borderline hypertension over a period of 20 years. After 10 years, the hemodynamics changed from high cardiac output to high resistance, but the baseline blood pressure did not increase. After 20 years, the majority of previously borderline subjects developed clinical hypertension due to a further increase of the vascular resistance. The decrease of cardiac output after 20 years was mediated by both a lower heart rate and a decrease of stroke volume.

MECHANISM OF HEMODYNAMIC TRANSITION

Hemodynamic autoregulation is the ability of an organ to maintain a steady, optimal flow by varying its resistance. "Total body autoregulation" is one mechanism that could decrease the cardiac output and increase the vascular resistance in the course of developing hypertension. The concept of total body autoregulation proposed by Guyton and Coleman[26] describes hemodynamic events observed after volume expansion. In partially nephrectomized animals, salt and water overload leads to increased cardiac output. This elevated flow exceeds the metabolic needs of various organs in the body and triggers an autoregulatory increase of vascular resistance and a higher blood pressure. The higher pressure causes enhanced diuresis, which in turn leads to restitution of a normal blood volume and a return of the cardiac output into the normal range.

In borderline hypertension, it is likely that this sequence fails to occur. Whereas renal sympathetic activation in borderline hypertension may lead to a tendency for acute fluid retention,[27] there is no evidence for a volume expansion in borderline hypertension. On the contrary, plasma volume in borderline hypertension is decreased.[28] Further, total body autoregulation is triggered only under conditions of "luxury perfusion," e.g., when the flow exceeds the metabolic demands of the body. The relationship between basal flow and metabolic demands in humans can be assessed from the relationship between cardiac output and resting oxygen consumption. In patients with hyperkinetic borderline hypertension, both the cardiac output and oxygen consumption are elevated.[3-5] Under these conditions the stimulus for total body autoregulation is absent.

Transition from a high cardiac output to a high resistance state in the course of hypertension can best be explained by altered target organ responsiveness. Prolonged exposure to increased sympathetic drive decreases the chronotropic and inotropic β-adrenergic responsiveness of the heart.[29,30] A decrease of β-adrenergically mediated vasodilation in hypertension has also been reported.[31] A further mechanism that, combined with decreased β-adrenergic responsiveness, may lead to the normalization of the cardiac output in the course of hypertension, is a decrease of stroke volume. Lund-Johansen[4] found that subjects with borderline hypertension do not adequately increase their stroke volume during exercise. The limitation of the stroke volume is particularly evident in the "normokinetic" (normal cardiac output) subgroup of patients with borderline hypertension. Such patients have lower than normal resting stroke volume, and this decrease is greatly accentuated after autonomic blockade of the heart with injections of propranolol and atropine.[29] The stroke volume in such a "denervated" heart depends solely on the end diastolic stretch. Since cardiac filling, evidenced by total blood volume and the cardiopulmonary portion of the blood volume, were not decreased, a pressure-induced decrease in cardiac compliance is most likely responsible for low stroke volume in these patients.

The same factors that lead to lower cardiac output are also conducive to the progressive elevation of vascular resistance in the course of hypertension. Longstanding blood pressure elevation causes hypertrophy of the medial layer of the arteriolar wall. The thicker media encroaches upon the lumen of the vessel, thereby changing the wall to lumen ratio. During vasoconstriction, the wall of the hypertrophic resistance vessels encroaches upon the lumen even more than in the relaxed state, and the increase of resistance is greatly exaggerated. This renders the resistance vessels hyperresponsive to all vasoconstrictive stimuli, a sequence described in detail by Folkow.[32] The degree of cardiac and vascular hypertrophy depends also on various "trophic" factors in addition to blood pressure. Sympathetic stimulation is a recognized vascular trophic factor,[33] and increased vasomotor tone in borderline hypertension may be, in its own right, conducive to early vascular hypertrophy. The presence of an altered wall to lumen ratio in the early phases of hypertension has been well documented[34] and these changes contribute to the maintenance of increased vascular resistance. It is conceivable that the enhanced vascular resistance is also due in part to decreased β- and enhanced α-adrenergic responsiveness, as proposed by Buhler et al.[31]

DECREASE OF SYMPATHETIC TONE IN THE COURSE OF HYPERTENSION

Decreased β-adrenergic responsiveness and decreased stroke volume, combined with the structurally increased vascular responsiveness, provide a plausible explanation for the transition from high cardiac output to elevated vascular resistance in the evolution of hypertension. However, an explanation is also needed for the parallel decrease of sympathetic tone. As hypertension advances, sympathetic activity is less evident. In a review of literature, Goldstein[35] found venous plasma norepinephrine to be elevated only in younger patients with borderline hypertension. Similar conclusions can be derived from the work of Esler et al.[15] Norepinephrine spillover rates are characteristically increased in younger patients, whereas spillover rates in older hypertensives are similar to those in normotensive individuals. Cardiac output and heart rate differences between borderline hypertensives and normotensive individuals decline with age. In our first study, a significant elevation of cardiac output and heart rate was seen only in patients younger than 45 years.[5]

Epidemiologic and clinical data strongly suggest that patients with borderline hypertension eventually develop a more severe, established hypertension. Why would the sympathetic tone change from elevated to apparently normal values during transition from borderline hypertension to established hypertension? We recently postulated an hypothesis that provides the necessary framework to explain this transition.[36] The hypothesis is based on numerous observations about the "blood-pressure-seeking" property of the CNS. Whereas the ultimate purpose of all circulatory control systems is to provide an adequate blood flow, it appears that the CNS subserves the circulation by regulating the blood pressure. This conclusion is reached from the analysis of numerous central blood pressure responses (mental stress, response to noise, isometric exercise, stellate ganglion stimulation, hindquarter compression in dogs). In all these situations it is possible to alter the underlying hemodynamics without changing the blood pressure response. For example, the increase of cardiac output with mental stress can be abolished with β-adrenergic blockade without affecting the magnitude of the blood pressure response.[37] Similarly, hemodynamic response to noise, normally associated with increased vascular resistance, can be converted with vasodilators into increased cardiac output without affecting the magnitude of the blood pressure response.[38] It is important to realize that during these pharmacologic interventions the underlying amount of cardiac output varied a great deal, but the blood pressure response was precisely regulated. This implies that feedback to the CNS must be related to the achieved pressure. If this is true, then the amount of neuronal firing needed to achieve a given pressure greatly depends on the responsiveness of peripheral organs. Due to an altered wall to lumen ratio, the arterioles in advanced hypertension are hyperresponsive to all vasoconstrictive stimuli,[39] and less sympathetic tone is needed to achieve the same blood pressure elevation. Within the context of the blood-pressure-seeking property of the brain, the observed sequence of events in borderline and advanced hypertension is to be expected. Accepting that as hypertension advances the vascular responsiveness becomes enhanced, if the CNS seeks a higher pressure, it can achieve that pressure increase in advanced hypertension with less sympathetic firing. The primary mechanism of blood pressure elevation may still be neurogenic, but due to changes of the vascular responsiveness, the absolute sympathetic tone will not be increased.

CAUSES OF AUTONOMIC ABNORMALITY IN HYPERTENSION

Behavioral research into the causes of enhanced sympathetic tone in hypertension took two directions. The "reactivity" research is based on observations of increased responsiveness to mental stress. There is substantial evidence that blood pressure response to mental stress is exaggerated in patients with borderline hypertension[40] and in offspring of hypertensive parents.[41] However, the responses to physical stressors in borderline hypertension are normal.[42] Also, blood pressure oscillation during 24-hour blood pressure monitoring is not exaggerated in borderline hypertension.[43] This speaks against a generalized CNS inability to regulate ANS blood pressure oscillations in hypertension. The notion that permanent hypertension occurs through a summation of exaggerated and frequent pressor episodes has no support in actual fact.

The other direction of research into behavioral causes assumes that the increased sympathetic tone is a product of an habitual style of interaction with the environment. Subjects with certain personality patterns may be more alert and vigilant, and this might cause a steady (not episodic) central activation of the sympathetic nervous system. A tendency to "hold anger in" has been described in subjects with higher blood pressure readings.[44] Inability to express anger is a particular characteristic of subjects with "sustained" (both at home and in the physician's office) blood pressure elevation, whereas increased anxiety is found in patients with "office" hypertension.[45] Subjects with borderline or mild hypertension are also known to be submissive to other people.[13,46] Unfortunately, these personality factors have not been evaluated in a prospective fashion to determine whether they can be found prior to the development of elevated blood pressure values.

Our recent studies in Tecumseh[47] suggest that the sympathetic activation in borderline hypertension is part of a very complex pathophysiologic picture. In addition to having faster heart rates, subjects with borderline hypertension tend to be overweight and have higher plasma insulin, cholesterol and triglyceride levels, whereas the high-density lipoproteins are decreased. Finding the primary aberration in this intimately intertwined set of abnormalities may be very difficult. For example, one recently proposed theory holds that the abnormality may reside in the dietary behavior of subjects with hypertension. Increased carbohydrate intake may lead to excessive insulin release, and this in turn may stimulate the CNS to increase the sympathetic discharge.[48] Interaction between sodium sensitivity, insulin resistance and sympathetic overactivity has also been postulated.[49] From a narrow frame of reference (behavioral medicine), investigations of the etiology of the increased sympathetic drive in hypertension are widening to include complex interdisciplinary research. At the present we are far from a definitive answer.

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Pharmacologic Characterization of Beta Blockers With Special Reference to the Significance of Nonspecific Membrane Effects

Shoichi Imai, MD

Along with the beneficial effects of β blockers in the ischemic derangements of myocardial energy metabolism are nonspecific membrane effects, which are thought to derive from the physicochemical interaction of the drugs with the cell membrane. These interactions are observed in various forms (e.g., membrane stabilizing action, quinidine-like action, cardiodepressant action), depending on the intensity of the interaction and on the method used for their detection. There may be still other manifestations that have not been detected so far, owing to our ignorance of their existence and our lack of an adequate method for their detection. The importance of the presence of specific chemical moieties in certain β blockers with ability to trap peroxy radicals is also discussed.

(Am J Cardiol 1991;67:8B–12B)

Beta blockers specifically bind to the β-adrenoceptor, blocking the actions of both endogenous and exogenous adrenergic agonists. Some β blockers also possess partial agonist activity (PAA). Generally, β blockers are classified by whether they are selective for β_1- or β_2-adrenoceptors and whether they have PAA.

Most, if not all, therapeutic effects of these agents result from the blockade of the β_1-adrenoceptor. Nonselective blockers act on both types of receptor, but confer therapeutic benefits only through β_1 blockade; their β_2 blockade may, in fact, have detrimental effects. Beta blockers with PAA may exert beneficial effects on plasma lipoproteins.

Some β blockers exert their effects by influencing the cell membrane in an unspecific manner. What follows is a discussion of these nonspecific membrane effects.

NONSPECIFIC MEMBRANE EFFECTS

The ability of β blockers to reduce infarct size has been demonstrated both in vitro and in vivo. In addition, β blockers lessen certain phenomena associated with irreversible damage during ischemia and/or reperfusion: accumulation of intracellular and intramitochondrial calcium, deterioration of mitochondrial oxidative phosphorylation, depletion of energy-rich phosphate compounds, and reduction of intracellular pH and intracellular accumulation of free fatty acids and some of their metabolites. The mechanisms of these cardioprotective actions are still not clear. They can be explained in part by catecholamine antagonism, as catecholamine depletion prior to anoxia or ischemia in isolated heart preparations leads to better recovery of the hearts. However, beneficial effects can be observed even in isolated perfused heart preparations with very low secretion of catecholamines[1] relative to the situation in vivo where prior chemical sympathectomy or depletion of catecholamines by reserpine did not result in protective effects.[2] Thus, it is clear that nonspecific membrane effects must be considered in certain experimental models.

PHYSICOCHEMICAL PROPERTIES

Levy[3,4] was the first to show that the nonspecific properties of β blockers may be related to their physicochemical properties. In a search for mechanisms underly-

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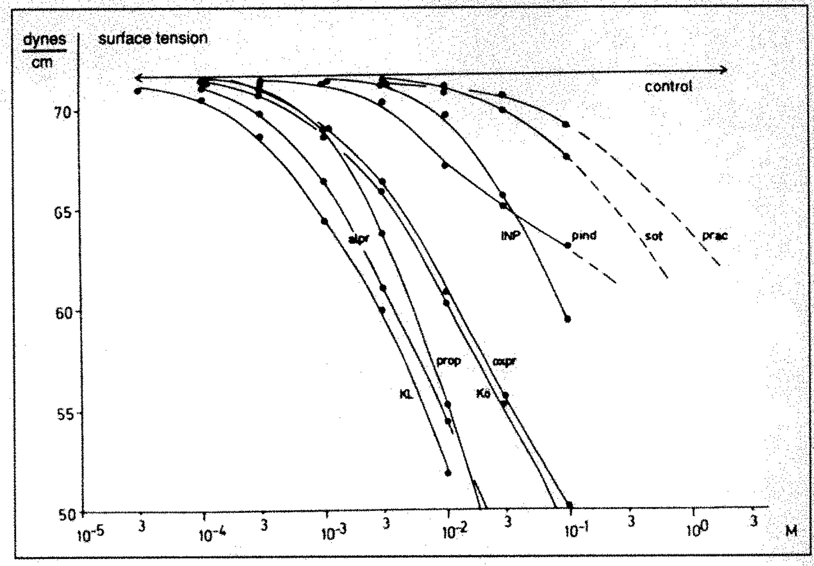

FIGURE 1. Surface tension-lowering effects of β blockers in Krebs-Ringer bicarbonate buffer, pH 7.2. Each point represents the mean of 2 experiments. The surface tension of the buffer solution is taken as control. Alpr, alprenolol; INP, INPEA; KL, KL 255; Kö, Kö 592; oxpr, oxprenolol; pind, pindolol; prac, practolol; prop, propranolol; sot, sotalol. (Reprinted with permission from *Arch Pharmacol.*[7])

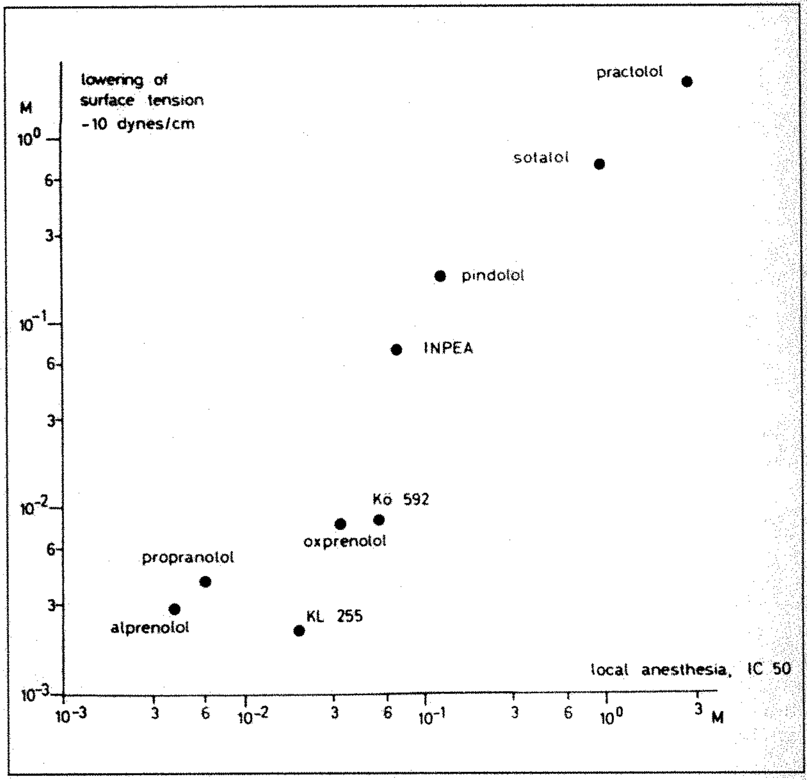

FIGURE 2. Correlation between local anesthetic potency and surface activity of β blockers. Incubation time = 10 min. (Reprinted with permission from *Arch Pharmacol.*[7])

ing the local anesthetic effect of several β-blocking agents, he determined the ability of several β blockers to lower surface tension; the relation between the ability to lower surface tension of an aqueous solution and local anesthetic actions had previously been shown in a homologous drug series by Skou[5] and Watson.[6]

Hellenbrecht et al[7] reevaluated the correlation between physicochemical characteristics and nonspecific biologic effects of β-blocking agents. They correlated the surface tension-lowering effects as well as the octanol/water partition coefficient of β blockers to the local anesthetic activity assayed in the sciatic nerve of the frog. They also studied the correlation to the depression of the myocardial conduction velocity of the isolated heart strips of the frog, because this parameter had been shown to mimic local anesthetic action on the heart muscle.[8] As is evident from Figure 1, these β blockers produced dose-dependent surface tension-lowering effects. KL 255 and alprenolol were the most potent, followed by propranolol, Kö 592 and oxprenolol. Nipenalol (INPEA) and pindolol were at least one order of magnitude less active. Sotalol and practolol showed only minimal effects even at

TABLE I Statistical Correlations Between the Physicochemical and Pharmacological Properties of 9 Beta Blockers.

	r	*p*
Surface activity vs partition coefficient	0.961	<0.001
Surface activity vs local anesthesia	0.948 (0.908)	<0.001
Surface activity vs myocardial conduction velocity	0.941 (0.925)	<0.001
Partition coefficient vs local anesthesia	0.972 (0.952)	<0.001
Partition coefficient vs myocardial conduction velocity	0.964 (0.959)	<0.001
Myocardial conduction velocity vs local anesthesia	0.985 (0.973)	<0.001
$\sum\pi$ calculated vs partition coefficient	0.976	<0.001
$\sum\pi$ calculated vs surface activity	0.922	<0.001
$\sum\pi$ calculated vs local anesthesia	0.930 (0.920)	<0.001
$\sum\pi$ calculated vs myocardial conduction velocity	0.932 (0.935)	<0.001

Correlation coefficients calculated from double log plots. Incubation period = 30 min; correlation coefficients in parentheses, incubation period = 40 min. (Reprinted with permission from *Arch Pharmacol.*[7])

TABLE II Oil/Water Partition Coefficients of Beta Blockers

Drugs	*n*-Octanol/Water Partition Coefficient
Propranolol	3.65
Alprenolol	2.61
Oxprenolol	2.18
Timolol	2.10
Metoprolol	2.15
Pindolol	1.75
Acebutolol	1.87
Nadolol	0.71
Atenolol	0.23

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concentrations of 0.1 *M*. A similar order of potency was observed as regards the other 3 parameters: alprenolol, propranolol and KL 255 comprised the most active group of agents; Kö 592, oxprenolol, INPEA and pindolol were intermediate; and sotalol and practolol were the least active. Figure 2 shows a highly significant correlation between surface tension-lowering activity and local anesthetic activity (the depression of the height of the action potential of the sheathed sciatic nerve of the frog). As shown in Table I, similar highly significant correlations were also found between the 4 parameters studied.

Thus, although the nonspecific membrane actions of these β blockers may be manifested as antiarrhythmic or quinidine-like, cardiodepressant, local anesthetic or membrane stabilizing, they all seem to derive from the same mechanism, i.e., a physicochemical interaction with the cell membrane. This interaction is dependent on the lipophilicity of the compounds, which can be quantified as oil/water partition coefficients (Table II). How a physicochemical interaction is defined has been dependent on the purpose of a particular investigation. For example, when researchers are studying β blocker effects on nerve conduction, they find "local anesthetic" action, while in the myocardium they appear as "quinidine-like" or cardiodepressant activity.

Other manifestations of nonspecific membrane action may exist, possibly produced at even lower concentrations.

Inhibition of the fall of myocardial intracellular pH during ischemia: Figure 3 shows the changes in the myocardial intracellular pH in the isolated perfused guinea pig heart with ^{31}P-NMR in our laboratory.[9] Although (+)-propranolol (10^6 *M*) confers β blockade 100-fold less potent than that of (−)-propranolol,[10] it was found to be as effective as (−)-propranolol in slowing the fall of pH and the depletion of energy-rich phosphate compounds during severe ischemia. Because the membrane-stablizing action of (+)-propranolol is known to be as potent as that of (−)-propranolol, we may assume that this protective effect stems from this membrane-stabilzing action. In the past, the therapeutic significance of the membrane-stabilizing effect was tempered by the rather high concentrations needed to elicit it. However, as discussed above, the membrane-stabilizing effect is just one manifestation of a β blocker's physicochemical interaction with the membrane. Therefore, the fact that the protective effect was observed at a concentration at which definite cardiodepressant effects were not still observable does not necessarily mean that the nonspecific membrane effects were not operative. Furthermore, the high lipophilicity of certain agents such as propranolol suggests that local concentration in the membrane may be high. In fact, the lipophilicity of the compound may be higher than currently thought. Recent studies[11] have indicated that tests with dihydropyridine Ca^{2+} antagonists in purified cardiac membrane lipid vesicles yielded a partition coefficient more than 3 orders of magnitude higher than that for a nonmembrane octanol/buffer system.

Specific chemical moiety in beta-blocker structure: Mak and Weglicki[12] studied the effects of β blockers and class I antiarrhythmic agents on free radical-mediated sarcolemmal lipid peroxidation by measuring the extent of lipid peroxidation by malondialdehyde formation. Five β blockers (propranolol, pindolol, metoprolol, atenolol and sotalol) inhibited sarcolemmal peroxidation in a concentration- and time-dependent manner. The order of potency was propranolol > pindolol > metoprolol > atenolol > sotalol. Thus, sarcolemmal peroxidation appears to follow the same order of potency as lipophilicity, with the exception of metoprolol.

Because β blockers are cationic amphiphiles—many of which have been found to form complexes with phos-

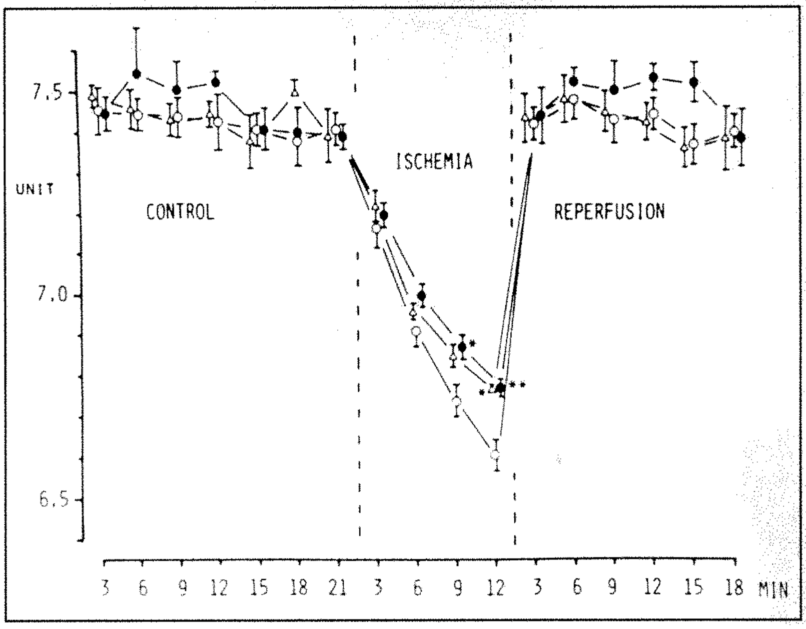

FIGURE 3. Effects of (−)- and (+)-propranolol on changes in intramyocardial pH as determined with ^{32}P-NMR during ischemia (12 min) and reperfusion. ○, control hearts (n = 6); •, (−)-propranolol (10^{-6} *M*)-treated hearts (n = 5); △ = (+)-propranolol (10^{-6} *M*)-treated hearts (n = 5). *, $p < 0.05$, **, $p < 0.01$ (vs control hearts). (Reprinted with permission from Arch Pharmacol.[7])

pholipids—their interactions with the sarcolemmal membrane might result in the formation of drug-lipid complexes, which are less susceptible to free radical attack. If this is the case, the efficacy of each agent may depend on the degree of drug-lipid complexing, which in turn depends on the lipophilicity of each agent. However, neither quinidine nor lidocaine—compounds that are relatively lipophilic (an octanol/water partition coefficient comparable with that of pindolol)—provided major inhibition of sarcolemmal peroxidation.

According to Mak and Weglicki,[12] conventional chain-breaking antioxidants are usually phenols or aromatic amines and owe their antioxidant activity to their ability to trap peroxy radicals inside the membrane. As all the β blockers have the aromatic resonance rings (in the case of propranolol it is a naphthalene moiety) that most classic oxidants have in common and that allow them to stabilize trapped radicals, the antioxidant actions of β blockers may be explained by this capability. In fact, 1-methoxynaphthalene (200 μ*M*) produced a protective effect approaching 50% to 60% that of propranolol.

Elucidation of the exact mechanisms by which β blockers, especially propranolol, protect against sarcolemmal peroxidation requires further study. The physicochemical properties are an important factor that must not be overlooked, but the presence of a specific chemical moiety or moieties seems to be equally important.

INTERACTION OF NONSPECIFIC MEMBRANE EFFECTS AND SPECIFIC BETA-BLOCKING EFFECTS

Marie et al[13] studied the cardioprotective effects of β blockers with various pharmacodynamic profiles in isolated perfused guinea pig hearts subjected to 20 minutes of anoxia. After 15 minutes of reoxygenation, the recovery of indices of cardiac flow was assessed. Nadolol, a β blocker without stabilizing action, produced a protective effect. However, (+)-propranolol produced similar protective effects, and (±)-propranolol conferred protection significantly greater than nadolol. As the membrane-stabilizing activity of (±)-propranolol is equivalent to that of (+)-propranolol and the β-blocking activity of (±)-propranolol was reported to be lower than that of nadolol,[14] these findings indicate the potentiation by membrane-stablizing activity of the protective effects of the β blocker. In this study (+)-propranolol and (±)-propranolol produced a significant negative chronotropic effect, but no change in cardiac flow and work indices; neither the indices of cardiac flow and work nor heart rate were changed by nadolol.

Lipophilicity is also an important determinant of pharmacokinetic properties. Lipophilic agents tend to be metabolized by the liver and reach all body compartments with relative ease, while hydrophilic ones tend to be excreted unchanged by the kidney and do not access the deeper compartments, such as the brain, as easily.

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Vasodilation, Not Cardiodepression, Underlies the Antihypertensive Effect of Beta-Adrenoceptor Antagonists

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Most antihypertensive drugs act by counteracting vasoconstrictor mechanisms and lower blood pressure by lowering vascular resistance. The β blockers, which have the unique ability to counteract cardiac sympathetic drive, seem to be a major exception to this. Moreover, their degree of cardiodepression is directly correlated with the initial sympathetic tone and also with their degree of intrinsic sympathomimetic activity (ISA). Cardiodepression initially evokes a baroreflex-mediated proportional rise in vascular resistance. As indicated by review of the literature, the antihypertensive effect of β blockers always parallels a decline in vascular resistance. Studying β blockers with different degrees of ISA in 50 hypertensive patients after minimizing cardiac sympathetic drive by strict bed rest showed that the initial effect of the drug is offset by a rise in vascular resistance proportional to the fall in cardiac output. After that, blood pressure always fell in parallel with vascular resistance, whatever the absolute level of cardiac output. In the long run, blood pressure and vascular resistance were always positively correlated, irrespective of the level of cardiac output. Thus, like all other antihypertensive agents, β blockers also lower blood pressure through interference with a vasoconstrictor mechanism.

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From the work of Lund-Johansen and others,[1] it appears that most categories of antihypertensive agents interfere with vasoconstrictor mechanisms, since most of them lower vascular resistance to some extent (Fig. 1). By definition, the classic vasodilators have a profound effect on vascular resistance, but part of their antihypertensive potency is offset by reflex cardiostimulation and renal sodium and water retention.

Diuretics, calcium antagonists, angiotensin-converting enzyme inhibitors and α_1-adrenoceptor blockers lower blood pressure in parallel with the ordinate in the flow resistance diagram, i.e., by vasodilation. The centrally acting drugs, such as α-methyldopa and clonidine, cause a global reduction in central sympathetic outflow, through which both cardiac output and vascular resistance are reduced.[2-4] The only exceptions to this "vasodilator rule" of antihypertensive drugs seem to be the β-blocking agents, of which propranolol has been the prototype for more than 20 years. For an effect on blood pressure comparable with that of the other classes of antihypertensive agents, these drugs seem to reduce cardiac output and not to reduce or even to increase vascular resistance. However, these overall pictures do not take into account the large individual variation in blood pressure response to the various drugs.

Already by 1972, Tarazi et al had demonstrated that in patients who showed the most pronounced long-term fall in blood pressure on propranolol, vascular resistance fell and cardiac output returned to pretreatment values.[5] Thus, with β blockers the difference between acute and more long-term effects must apparently be taken into account. This prompted us in 1982 to review the literature on the acute and long-term hemodynamic effects of β blockers in hypertension.[6] Special attention was given to the ancillary properties of β blockers, such as selectivity for β_1-receptors and partial agonist activity (PAA), also called intrinsic sympathomimetic activity (ISA). Potentially, β blockers with different ancillary properties may exert different effects on cardiac output and thereby modify the hemodynamic profile of the drugs.

EARLY DATA ON HEMODYNAMIC EFFECTS OF BETA BLOCKERS

Various reviews of the literature on 10 different β blockers have been published in detail.[6-14] The reviews

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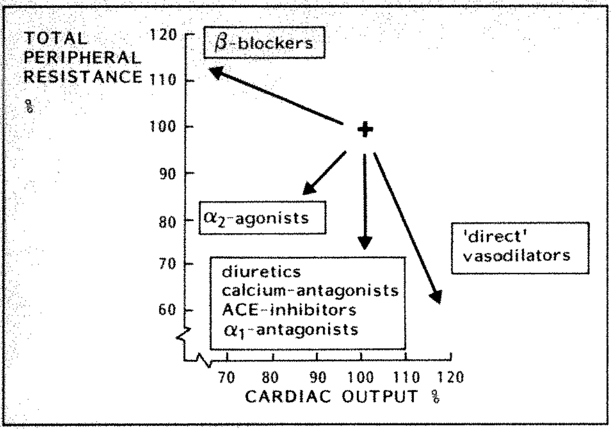

FIGURE 1. Relative effects of different categories of antihypertensive agents on cardiac output and total peripheral resistance in hypertension. The black cross indicates the situation before treatment.

TABLE I Partial Agonist Activity and Beta$_1$-Adrenoceptor Selectivity of 10 Beta-Adrenoceptor Antagonists

	Partial Agonist Activity (PAA)	Beta-Adrenoceptor Selectivity
Pindolol	+++	Beta$_1$ + beta$_2$
Practolol	++	beta$_1$
Alprenolol	+	Beta$_1$ + beta$_2$
Oxprenolol	+	Beta$_1$ + beta$_2$
Acebutolol	±	Beta$_1$
Penbutolol	±	Beta$_1$ + beta$_2$
Metoprolol	−	Beta$_1$
Atenolol	−	Beta$_1$
Propranolol	−	Beta$_1$ + beta$_2$
Timolol	−	Beta$_1$ + beta$_2$

+++ to ±, varying degrees of PAA; −, absence of PAA.

comprised 85 studies on 10 β blockers in a total of 912 patients. The ancillary properties of the 10 β blockers that were reviewed are given in Table I.

When given intravenously, the β blockers hardly have any effect on blood pressure despite profound effects on heart rate, cardiac output and vascular resistance (Figs. 2,3). It appears, however, that an inverse correlation exists between the degree of ISA of the various β blockers and their effects on the heart and vascular resistance. In the long run, despite their different ancillary properties, the β blockers have, on average, approximately equal antihypertensive efficacy. Between the initial phase of β blockade and the more chronic phase of treatment, cardiac output does not change for a given β blocker, which implies that any reduction in blood pressure can only be the result of a reduction in vascular resistance. In other words, β blockers, like other antihypertensive agents, seem to lower blood pressure by interference with a vasoconstrictor mechanism.

It must be taken into account, however, that since the different β blockers have such different effects on cardiac output, as determined by their degree of ISA, they have different effects on vascular resistance both acutely and chronically. Thus, the β blockers with sufficient ISA to maintain cardiac output do not initially evoke reflex vasoconstriction. During chronic treatment, vascular resistance will fall below pretreatment values. Beta blockers devoid of ISA will cause a major vasoconstriction, initially proportional to the degree of cardiodepression. Despite an adjustment of vascular resistance in the long run, on these drugs vascular resistance will remain elevated, often above pretreatment values.

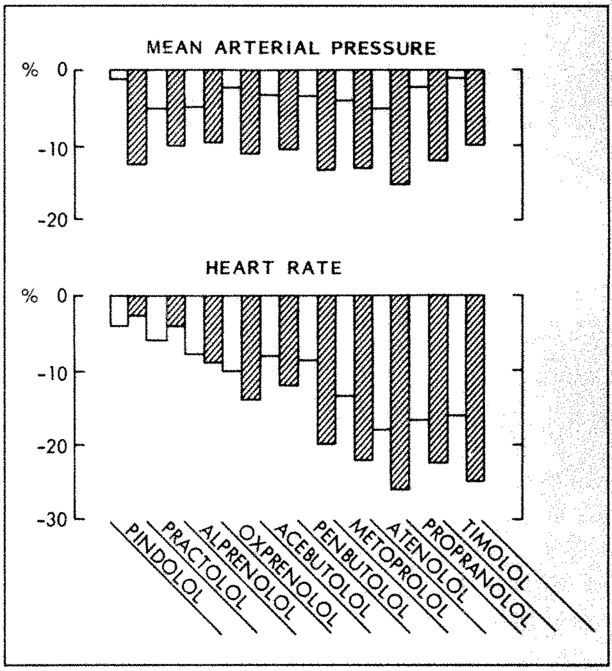

FIGURE 2. Effects of β blockers on mean arterial pressure and heart rate in hypertensive patients. Acute effects: Open bars. Long-term effects: hatched bars.

These data can be illustrated more clearly in a flow-resistance diagram (Fig. 4). Both acutely and chronically, cardiac output and vascular resistance are, by definition, inversely correlated for the different β blockers. The fall in blood pressure occurs for all drugs, always in parallel with the ordinate (i.e., by vasodilation). It should be noted that, acutely, the more pronounced the degree of ISA for a given β blocker, the closer it is in the diagram to the pretreatment point of cardiac output. Furthermore, it appears that cardioselectivity, either in the presence or in the absence of ISA, does not modify the hemodynamic profile of a β blocker. Apparently unopposed α-receptor-mediated vasoconstriction is not an important determinant of the hemodynamic profile of nonselective β blockers.

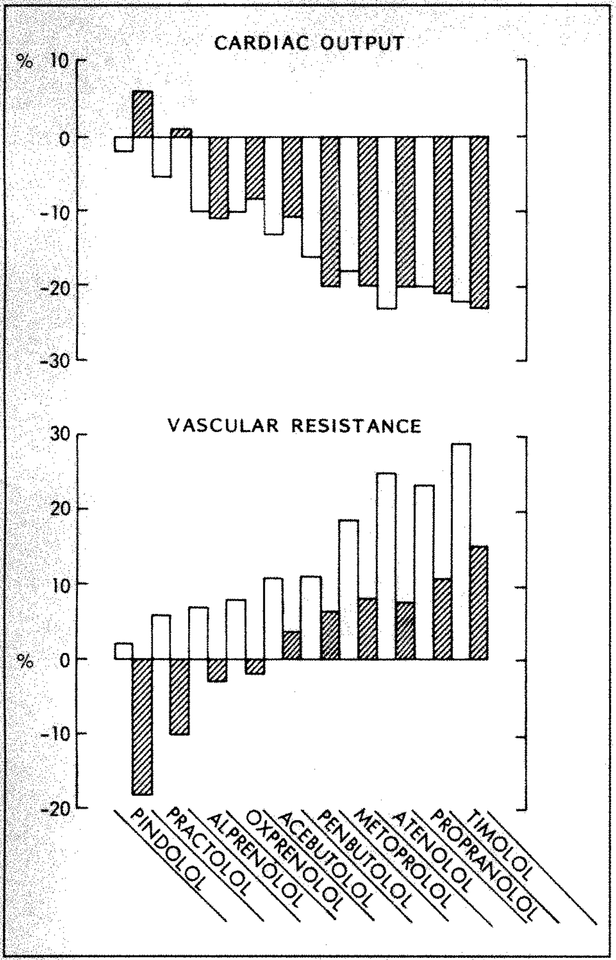

FIGURE 3. Effects of β blockers on cardiac output and vascular resistance in hypertensive patients. Acute effects: open bars. Long-term effects: hatched bars.

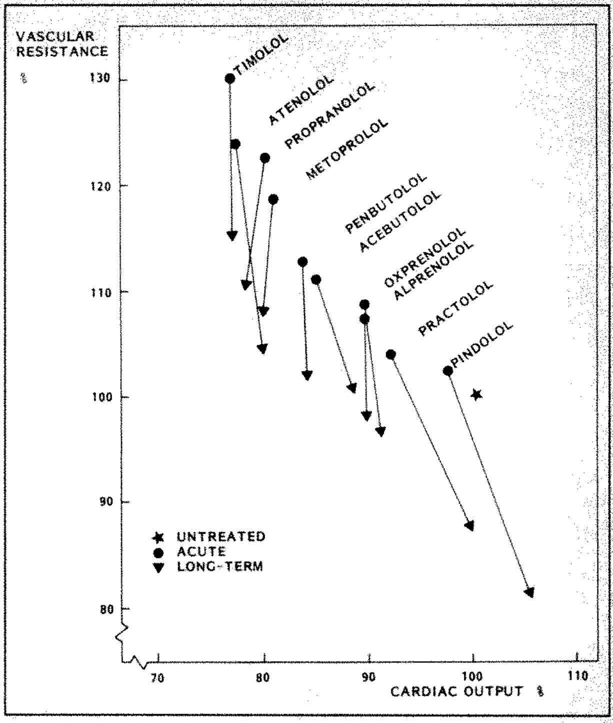

FIGURE 4. Hemodynamic interrelationships during acute (●) and long-term (▼) β blockade in hypertension. The asterisk indicates the situation before treatment.

TABLE II Beta Blockers Studied During 36 Hours of Bed Rest

	Partial Agonist Activity (PAA)	Beta-Adrenoceptor Selectivity	Dose	No. of Patients
Pindolol	+++	$\text{Beta}_1 + \text{beta}_2$	10 mg bid	10
Acebutolol	±	Beta_1	400 mg bid	10
Bopindolol	±	$\text{Beta}_1 + \text{beta}_2$	2 mg od	10
Atenolol	−	Beta_1	100 mg od	10
Propranolol	−	$\text{Beta}_1 + \text{beta}_2$	80 mg tid	10

+++ to ± = varying degrees of PAA; − = absence of PAA; bid = twice daily; od = daily; tid = three times daily.

One of the drawbacks of a literature review is that it combines data obtained in different protocols by different investigators. More importantly, since acute and long-term studies were separately analyzed, interpolation was made for the intermediate hemodynamic events. Thirdly, although only studies performed in supine resting patients were included, baseline periods varied from 10 minutes up to 1 hour in the different studies. Therefore we undertook a study in which we studied the onset of the antihypertensive effect of β blockers, minimized cardiac sympathetic drive by keeping the patients in bed for 36 hours, and compared the results of β blockers with different effects on cardiac output due to variable degrees of ISA.

OBSERVATIONS OF BETA BLOCKERS DURING ABSOLUTE BED REST FOR 36 HOURS

The protocol of the studies has been published in detail.[15-22] The patients were untreated for 2 weeks, then they were switched to placebo for 2 weeks. At the end of the second placebo week, the acute hemodynamic effects of the β blockers were studied for 24 hours while the patients had complete bed rest, which was preceded by 12 hours of bed rest overnight. The β blockers that were studied are shown in Table II.

After 24 hours, the 5 β blockers had on average an almost identical effect on arterial pressure (Fig. 5). Initially, cardiac output fell with all drugs, except on pindolol with its pronounced degree of ISA. In the phase of cardiodepression, vascular resistance rose and blood pressure did not change. A gradual fall in blood pressure was observed on all β blockers between 2 and 5 hours after dosing. The fall in blood pressure was caused in all cases by a reduction in vascular resistance. The antihypertensive and vasodilator effect of the drugs was associated

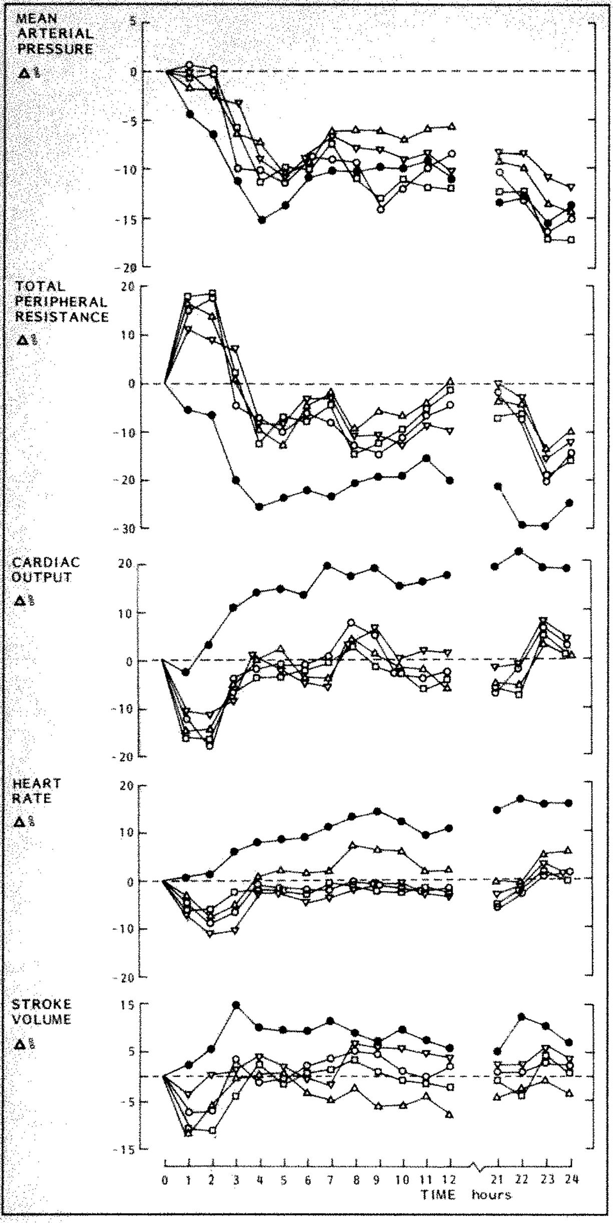

FIGURE 5. Hemodynamic changes during the onset of the antihypertensive effect of 5 β blockers. The drugs were administered orally at time 0. • = pindolol; ○ = propranolol; □ = acebutolol, △ = atenolol, ▽ = bopindolol.

with return of cardiac output, heart rate and stroke volume to baseline values, and for pindolol, above baseline values. After 24 hours, the antihypertensive effect of all β blockers was associated with a reduction of vascular resistance below pretreatment level. However, at any level of blood pressure, cardiac output was higher and vascular resistance was lower on pindolol as compared to the other drugs. Thus, all β blockers exerted their antihypertensive effect through vasodilation. The degree of vasodilation depends on cardiac sympathetic drive and ISA as determinants of the magnitude of the effect on cardiac output.

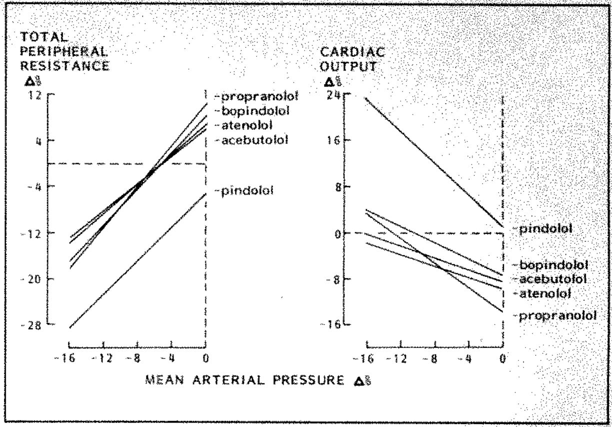

FIGURE 6. Interrelations between changes in mean arterial pressure and changes in total peripheral resistance or cardiac output during the gradual onset of the antihypertensive effect of 5 β blockers over 24 hours.

HEMODYNAMIC INTERRELATIONS AND ADAPTATIONS DURING BETA BLOCKADE

For all 5 β blockers, highly significant correlations emerged over the 24-hour period between arterial pressure on the one hand and vascular resistance and cardiac output on the other (Fig. 6) ($p < 0.001$ in all cases). This explains the lower pressure, the lower vascular resistance and the higher cardiac output. Therefore, if anything, a low cardiac output during β blockade prevents rather than causes a reduction in blood pressure. The regression lines were not different for the β blockers, with the exception of pindolol, which showed higher values of cardiac output and lower values of vascular resistance for any value of blood pressure.

How to explain the increments in cardiac output, heart rate and stroke volume when blood pressure and vascular resistance start to fall after starting β blockade? It has been demonstrated that changes in heart rate, cardiac output and stroke volume after vasodilation during β blockade depend on vagal withdrawal and on an increase in venous return.[23] Thus, during the vasodilator phase of the β blockers, the initial hemodynamic changes are offset by interference of the arterial baroreflex (Fig. 7).

DISCUSSION

Most antihypertensive agents lower blood pressure by lowering vascular resistance. Beta blockers seem to be an exception. The efficacy of all antihypertensive agents is independent of sympathetic drive.[1] However, the cardiac effects of β blockers depend both on cardiac sympathetic drive and on degree of ISA. Through interference of the baroreflex, the hemodynamic profile of β blockers is modified at different levels of sympathetic activity. Thus, β blockers may or may not increase peripheral vascular

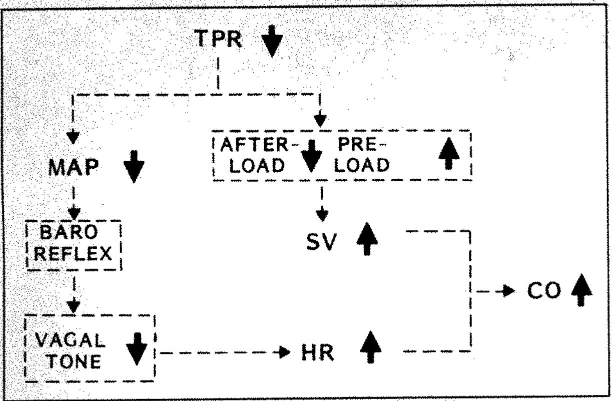

FIGURE 7. Hemodynamic adaptations during β blockade. TPR = total peripheral resistance; MAP = mean arterial pressure; SV = stroke volume; HR = heart rate; CO = cardiac output.

resistance in hypertension, depending on the duration of β blockade, the magnitude of the antihypertensive response, their degree of ISA and, last but not least, the level of sympathetic drive. Under all circumstances, however, it is the decrease in vascular resistance that is responsible for the antihypertensive efficacy of these drugs. In conclusion, like all other antihypertensive drugs, β blockers lower blood pressure by interference with a vasoconstrictor mechanism. The exact nature of this vasodilator mechanism of β blockers is still very much disputed. Central β receptors, presynaptic β receptors at the vascular wall and postsynaptic β receptors on juxtaglomerular cells within the kidney are all possibilities for explaining the vasodilator action of β blockers.

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Blood Pressure During Sleep: Antihypertensive Medication

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To investigate whether excessive reduction of blood pressure (BP) by antihypertensive medications correlates with myocardial infarction, especially during sleep in elderly patients, we used telemetry and cuvette dye-dilution methods to assess the direct BP and the hemodynamics of 68 inpatients with essential hypertension during wakefulness and sleep. There were 25 patients $\geq$60 years old (OH-group) and 43 were $\leq$59 years old (YH-group).

Of the OH-group, 36% showed high BP during the day, with marked decreases (minimum BP <110/70 mm Hg) during sleep. Average cardiac index (CI) of the OH-group was low during wakefulness and extremely low during slow-wave sleep. Changes of mean BP in the OH-group correlated with changes in total peripheral vascular resistance index (TPRI) during sleep, but this correlation was not observed in the YH-group.

The antihypertensive effects on nocturnal BP of the various medications was: central adrenergic inhibitors $\leq$ β blockers with intrinsic sympathomimetic activity $\leq$ α ($\alpha\beta$) blockers $\leq$ angiotensin-converting enzyme inhibitors $\leq$ calcium antagonists.

Because BP and CI were found to be very low and TPRI seems to play an important role in BP regulation in sleeping elderly patients, excessive antihypertensive medication may be harmful to this subgroup. However, because the effects on nocturnal BP differ among various antihypertensive treatments, further research is required on the relation between antihypertensive medication and the hemodynamics of sleeping elderly hypertensive patients.

(Am J Cardiol 1991;67:18B–25B)

At present, casual blood pressure (BP) is still used as the standard for clinical hypertensive evaluation. However, casual BP does not correlate favorably with average 24-hour BP values[1,2] and casual BP cannot predict BP values during sleep. The mortality rates from myocardial infarction (MI) and cerebral infarction induced by excessive reduction in BP from antihypertensive agents have been reported to be relatively high[3,4] in elderly hypertensive patients. Previous studies[5] have determined that older patients ($\geq$60 years) who had not been taking antihypertensive agents showed a high incidence of MI during the day. This result has been confirmed in other reports.[6,7] However, in older patients who had been taking antihypertensive agents (chiefly diuretics), there was a frequent occurrence of MI during the night, especially between 1:00 AM and 3:00 AM.[5] The reason for this result is unclear, but the antihypertensive agents may have had some effect on the incidence of MI during the night. Because management of BP during sleep, when BP is at its lowest level, is vitally important in the care of elderly hypertensive patients, we measured their hemodynamics during sleep and then examined the effects of various antihypertensive agents on their nocturnal BP values.

SUBJECTS AND METHODS

Measurement of hemodynamics: The subjects of the study were 68 inpatients with mild to moderate essential hypertension (41 men, 27 women), aged 22 to 78 years, who were taking no antihypertensive medication. Secondary hypertension was ruled out in all of the subjects when they were examined on admission. The patients all fell into World Health Organization categories I and II, showing average casual values of diastolic blood pressure (DBP) between 90 and 115 mm Hg and systolic blood pressure (SBP) between 140 and 220 mm Hg. The patients were divided into a younger group of 43 patients (25 men, 18 women) <60 years of age and an older group of 25 patients (16 men, 9 women) $\geq$60 years. A normotensive control group consisted of 23 volunteers (13 men, 10 women) aged 25 to 58 years with normal BP values (casual SBP <140 mm Hg, casual DBP <85 mm Hg) (Table I). All subjects were given sufficient explana-

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TABLE I BP Values of H-Type, L-Type, W-Type Hypertensive Patients and Normotensive Subjects

		Patients with Mild or Moderate Essential Hypertension					
		Younger Group		Older Group			Normotensives
		H-Type	L-Type	H-Type	L-Type	W-Type	NT
No. (male/female)		22 (12/10)	13 (8/5)	12 (8/4)	9 (5/4)	12 (8/4)	23 (13/10)
Age (years old)		41 ± 11.8	42 ± 11.7	65 ± 3.4	63 ± 2.9	42 ± 14.9	42 ± 12.0
Casual	SBP (mm Hg)	172 ± 7.5	168 ± 9.2	180 ± 12.0	174 ± 9.5	158 ± 11.0‡	126 ± 8.1
	DBP (mm Hg)	98 ± 5.1	95 ± 4.8	94 ± 7.0	93 ± 8.9	92 ± 4.1‡	76 ± 7.4
	MBP (mm Hg)	123 ± 6.3	119 ± 7.0	122 ± 9.5	120 ± 9.2	114 ± 9.8‡	93 ± 7.8
Waking	SBP (mm Hg)	160 ± 7.7	153 ± 11.0*	169 ± 16.0	159 ± 11.0	135 ± 2.2‡	124 ± 8.4
	DBP (mm Hg)	97 ± 5.9	94 ± 5.5	93 ± 8.4	86 ± 10.0	84 ± 4.3‡	75 ± 7.4
	MBP (mm Hg)	118 ± 6.8	113 ± 8.4	117 ± 12.0	110 ± 10.0	101 ± 3.3‡	91 ± 7.9
Nighttime	SBP (mm Hg)	140 ± 110	129 ± 4.7†	144 ± 16.0	123 ± 19.0*	120 ± 8.7‡	103 ± 9.5
	DBP (mm Hg)	86 ± 8.5	79 ± 4.2†	81 ± 7.0	66 ± 11.0†	75 ± 6.3‡	59 ± 9.3
	MBP (mm Hg)	104 ± 9.9	95 ± 4.5†	102 ± 12.0	85 ± 15.0†	90 ± 7.5‡	73 ± 9.4
Minimum	SBP (mm Hg)	128 ± 8.2	106 ± 4.9†	131 ± 11.0	104 ± 6.7‡	99 ± 5.3*	91 ± 9.4
	DBP (mm Hg)	77 ± 8.1	66 ± 6.4‡	71 ± 8.3	60 ± 9.1†	59 ± 5.4†	52 ± 9.2
	MBP (mm Hg)	95 ± 8.1	79 ± 5.7‡	91 ± 9.6	75 ± 7.9‡	72 ± 5.3*	65 ± 9.3
24 hours	SBP (mm Hg)	156 ± 7.0	141 ± 9.1‡	165 ± 13.3	143 ± 18†	129 ± 4.4†	119 ± 8.0
	DBP (mm Hg)	96 ± 5.8	88 ± 7.7†	96 ± 7.7	86 ± 10*	80 ± 4.8‡	69 ± 8.3
	MBP (mm Hg)	116 ± 6.4	106 ± 8.2‡	119 ± 10.5	106 ± 14*	96 ± 4.6‡	85 ± 8.1
	Mean ± SD	vs. H-TYPE		vs. H-TYPE		vs. NT	

*p <0.05; †p <0.01; ‡p <0.001.
SBP = systolic BP; DBP = diastolic BP; MBP = mean BP.

tions of the test protocol, and their consent was obtained prior to the study.

Brachial intra-arterial BP and electrocardiograms were measured throughout the 24 hours by a telemeter[8] and recorded on magnetic tape, respectively, and the beat to beat BP and heart rate were analyzed by computer. Nighttime (9:00 PM to 6:00 AM) electroencephalograms (EEG), electro-oculogram and respiratory rate were monitored.

A frequency distribution of nighttime (10:00 PM to 6:00 AM) BP was obtained, and the 0.5% lower limit value was taken as the minimum BP during sleep (BP_{min}). Two 3-way stopcocks were attached to the catheters: one was inserted in the artery and another in the antecubital vein. Minute amounts of heparin-saline solution (2 ml/hour) were infused into these catheters using portable microinfusion pumps to prevent the blood from coagulating in the catheters.

Measurement of cardiac output was carried out in some patients while they were awake (in supine position) and during sleep (slow-wave [stage III-IV], as judged from the EEG[9]). To do this, the 3-way stopcock on the arterial side was connected to a cuvette dye-densitometer (ERMA Dye-Densitograph EW-90); 5 mg of indocyanine green in 20 ml physiological saline was then rapidly infused into the cock on the venous side, a dye-dilution curve was determined and cardiac output was automatically calculated by the computer in this device. Measurements were excluded in subjects who awoke while sleep values were being taken. Total peripheral vascular resistance index (TPRI) was determined by dividing cardiac index (CI) by mean BP at the time of measurement.

Examining effects of antihypertensive medications on nocturnal BP: Eighty-five patients with mild to moderate essential hypertension were included in this study. The BP was measured in hospitalized patients by the direct method, using a compact portable recorder with digital memory unit[10] (3 × 8 × 13 cm in size, 400 g in weight). Outpatients were evaluated by the indirect method, using an automatic BP recorder[11] (4 × 6.5 × 14 cm in size, 390 g in weight; TM 2420 of A&D Co.). The 24-hour BP measurement was performed for the first time after 1 week of placebo administration; then various antihypertensive agents were administered at their normal dosage regimens. Table II shows the number of patients and average ages for administration of various antihypertensive agents. BP was measured for the second time 7 to 10 days later. Direct BP was measured every 10 seconds, and indirect BP was measured every 15 to 30 minutes for periods of 24 hours or more.

Analysis of these results was carried out by computer (PC 9801, NEC) in all cases, and average values for mean BP (MBP) during the nighttime (10:00 PM to 6:00 AM) and during the daytime (6:00 AM to 10:00 PM) were calculated before and after antihypertensive medication administration. The rate of reduction in nighttime blood pressure (n) was also determined. Calculation was carried out using the following equation (night MBP before

TABLE II Effect of Various Antihypertensive Agents on Nocturnal BP

Antihypertensive Agents	No.	Age (yrs)	Dose (mg)	*d* (%)	*n* (%)	*n*/*d*
Placebo	4	36 ± 10	0 TID	+2.5 ± 2.4	+0.4 ± 2.4	
Adrenergic inhibitor						
Central: Guanfacine	3	55 ± 4.5	1.5 QD†	−15.4 ± 3.6	−10.2 ± 3.4	0.66
β-blocker:						
Propranolol-LA	4	46 ± 8	120 QD	−16.4 ± 3.2	−11.6 ± 2.1	0.71
Atenolol	12*	53 ± 8	50–100 QD	−9.8 ± 2.1	−7.3 ± 1.6	0.74
Bopindolol	17*	53 ± 9	1–2 QD	−9.8 ± 2.4	−6.4 ± 1.7	0.65
α-blocker:						
Bunazosin	6	46 ± 7	2–3 TID	−10.4 ± 2.0	−11.3 ± 2.5	1.08
Prazosin	6	46 ± 7	2 TID	−5.0 ± 1.7	−2.8 ± 1.6	0.56
αβ-blocker:						
Dilevalol	3	48 ± 10	100 TID	−13.7 ± 3.9	−14.9 ± 3.8	1.09
Labetalol	3	45 ± 11	150 TID	−17.4 ± 2.9	−17.3 ± 5.9	1.00
Calcium antagonist:						
Diltiazem	7	54 ± 9	60 TID	−15.2 ± 4.0	−18.3 ± 4.2	1.20
Nicardipine	7	54 ± 9	20 TID	−13.2 ± 3.8	−15.0 ± 3.9	1.14
Nitrendipine	3	58 ± 7	20 QD	−7.7 ± 1.1	6.8 ± 1.6	0.89
ACE inhibitor:						
Captopril	4	48 ± 10	25 BID	−12.5 ± 3.5	−12.1 ± 1.7	0.97
Enalapril	3	50 ± 8	2.5–10 QD	−11.7 ± 2.2	−9.5 ± 2.0	0.81
Ramipril	3*	46 ± 10	1.25–10 QD	−11.0 ± 2.4	−9.1 ± 1.8	0.82

Mean ± SE; * indirect method; † administration before bedtime.
% change = MBP after treatment − MBP before treatment/MBP before treatment × 100%; *n* = % change during nighttime; *d* = % change during daytime.
ACE = angiotensin-converting enzyme; QD = daily; BID = twice daily; TID = three times daily.

treatment = average nighttime MBP prior to administration; night MBP after treatment = average nighttime MBP after administration):

$$n = \frac{\text{(night MBP after treatment} - \text{night MBP before treatment)}}{\text{night MBP before treatment}} \times 100\%$$

The rate of reduction in blood pressure during the daytime (*d*) was determined by the following equation:

$$d = \frac{\text{(daytime MBP after treatment} - \text{daytime MBP before treatment)}}{\text{daytime MBP before treatment}} \times 100\%$$

The ratio *n*/*d* was obtained as an index of the decrease in nighttime BP. Specifically, the smaller this ratio is below 1, the smaller is the rate of reduction in nighttime blood pressure compared to the rate of reduction in daytime blood pressure.

Significant differences within one group were calculated using the paired Student's *t*-test and those between the two groups were calculated using the unpaired *t*-test ($p \leq 0.05$ = significant).

RESULTS

Decrease in BP during sleep: Both the normotensive subjects and the hypertensive patients showed clear decreases in BP during sleep, but the decrease was more pronounced in some subjects (Fig. 1). The minimum nighttime BP values for the normotensive subjects were SBP = 91 ± 9.4 (SD) mm Hg, DBP = 52 ± 9.2 mm Hg and MBP = 65 ± 9.3 mm Hg. The mean + 2 SD upper limit values were SBP = 110 mm Hg, DBP = 70 mm Hg and MBP = 84 mm Hg. Daytime mean + 2 SD upper limit values were SBP = 141 mm Hg and DBP = 90 mm Hg (Table I).

Among the 68 patients with essential hypertension, 12 with average daytime BP values of SBP <140 mm Hg and DBP <90 mm Hg were thought to be nearly normotensive, like those having so-called white-coat hypertension (W-type), and were excluded from the present study. The patients with BP on waking of ≥140/90 mm Hg and minimum SBP <110 and minimum DBP <70 mm Hg were taken as the low night-BP type (L-type) and patients with values higher than these were taken as the high night-BP type (H-type) (Fig. 2).

Table I and Figure 2 show the number of patients and 24-hour BP values for each type in the younger and older groups. L-types accounted for 30% in the younger group and 36% in the older group, and the average minimum MBP for L-types was below the 2 SD upper limit value (84 mm Hg) for the normotensive group (Fig. 3).

Cardiac output and TPRI during sleep: Beginning with an original group of 42 subjects, cardiac output during sleep (sleep stages III-IV) was measured in 13 subjects in the younger group (8 men, 5 women; average age 46 ± 14 [SD]) and 14 subjects in the older group (8 men, 6 women; average age, 65 ± 4). The number of patients was small because the patients who had awakened during the investigation were eliminated.

The average CI in the older group was low during waking hours and extremely low during sleep (2.4 ± 0.4/

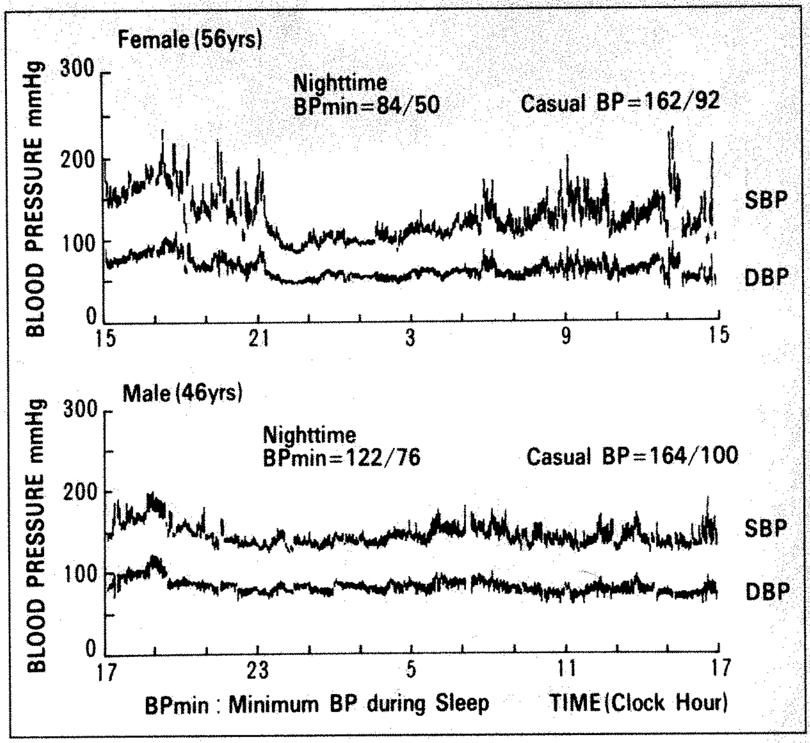

FIGURE 1. Time course trendgram of direct blood pressure during 24 hours. Both systolic blood pressure (SBP) and diastolic blood pressure (DBP) indicate 3-minute averages ± SD. *Top* shows a case of marked decrease in blood pressure during sleep, and *bottom* shows a case of no marked decrease in blood pressure during sleep. BP_{min} denotes lower 0.5% limit of blood pressure frequency distribution during nighttime.

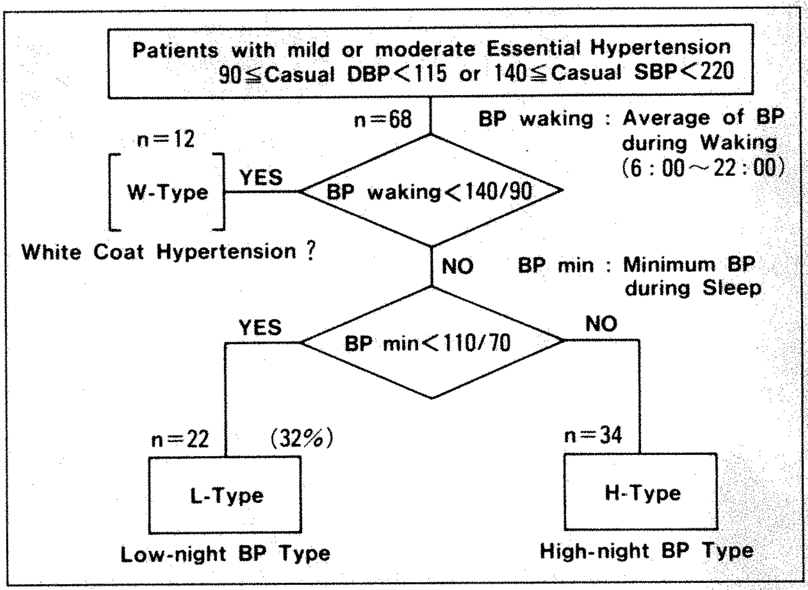
Patients with mild or moderate Essential Hypertension
90≦Casual DBP<115 or 140≦Casual SBP<220
n=68
BP waking : Average of BP during Waking (6 : 00～22 : 00)
n=12
W-Type
YES
BP waking<140/90
White Coat Hypertension ?
NO
BP min : Minimum BP during Sleep
YES
BP min<110/70
NO
n=22
(32%)
L-Type
Low-night BP Type
n=34
H-Type
High-night BP Type

FIGURE 2. Classification of patients with mild to moderate essential hypertension into 3 groups based on 24-hour blood pressure values.

2.1 ± 0.3 [SD] L/min/m^2), whereas CI in the younger group was 3.2 ± 0.4 and 2.6 ± 0.3, respectively. Although mean BP and mean BP reduction during sleep were comparable in the two groups, the decrease in CI during sleep was smaller in the older group than in the younger group ($p < 0.01$). TPRI decreased in the older group (48 ± 7 mm Hg/L/min/m^2 upon awakening versus 42 ± 7 during sleep; $p < 0.01$), but did not change in the younger group (35 ± 4 to 35 ± 3; NS).

In the older group, the correlation between reduction ratio (Δ%) of mean BP value and Δ% of TPRI value (Δ% = 100 [value during sleeping − value during waking]/value during waking) was significant ($r = 0.67$, $p < 0.05$), but the correlation between Δ% mean BP and Δ% CI was slight ($r = 0.26$, NS). In the younger group, a correlation was observed between Δ% mean BP and Δ% CI ($r = 0.65$, $p < 0.05$), but there was no significant correlation between Δ% mean BP and Δ% TPRI ($r = 0.04$, NS). These results suggest that CI plays an important role in BP changes from waking to sleeping in the younger group, whereas TPRI plays the principal part in maintaining BP in the older group.

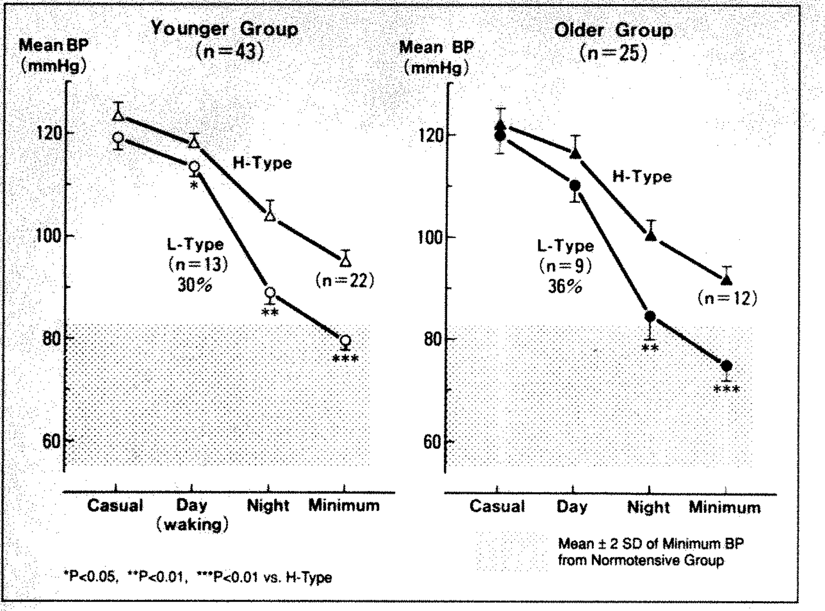

FIGURE 3. Reduction of mean BP during sleep in the younger group and the older group (L-type = low night-BP-type; H-type = high night-BP-type; minimum, lower limit of nighttime BP).

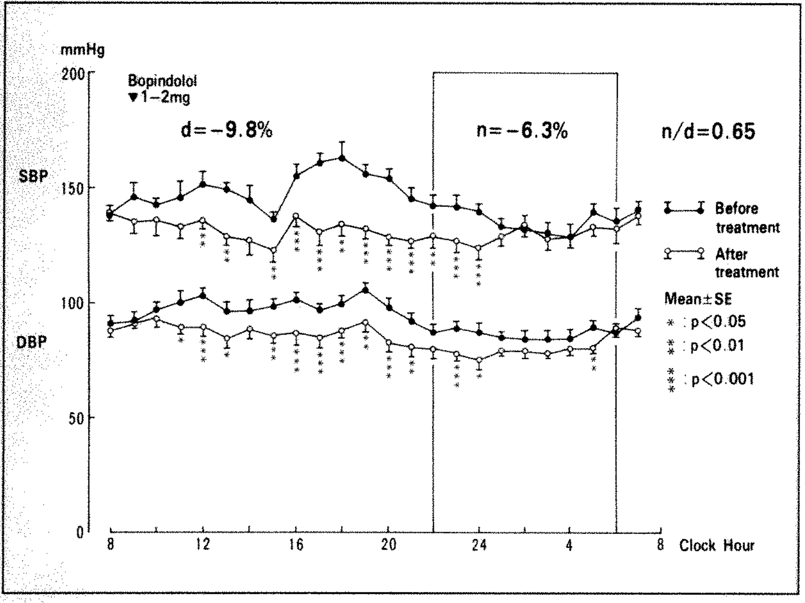

FIGURE 4. Effect of bopindolol on 24-hour blood pressure (indirect method; number of cases = 17; n = the rate of reduction in nighttime mean BP; d = the rate of reduction in daytime mean BP).

Effect on nocturnal BP of various antihypertensive agents: Table II shows *d*, *n*, and *d*/*n* values for various antihypertensive agents. The differences in *n*/*d* are probably dependent on the quantities and numbers of doses/day. The *d* and *n* values fluctuated in the −5% to 4% range before and after 1-week administration of the placebo. Guanfacine, a central-adrenergic inhibitor, showed a larger *d* than *n* even in single administration prior to nighttime, with an average *n*/*d* value of 0.66. Among the β blockers, on the other hand, bopindolol, which has intrinsic sympathomimetic activity (ISA), showed the lowest value for *n*/*d* (0.65) in single daily administration (Fig. 4, Table II).

The α_1 blocker bunazosin and the $\alpha\beta$ blockers dilevalol and labetalol all showed *n*/*d* averages of approximately 1. As for the calcium antagonists, diltiazem and nicardipine had *n*/*d* values of 1.20 and 1.14, respectively, showing the highest nocturnal antihypertensive effect, but single daily administration with nitrendipine showed a low value of 0.89. In the angiotensin-converting enzyme (ACE) inhibitors, twice-daily administration of captopril produced an *n*/*d* value of 0.97, higher than those seen with single daily administration of enalapril and ramipril.[12]

DISCUSSION

Although many points remain unclear concerning nighttime hemodynamics, it has long been known that BP decreases during sleep.[13-16] During one sleep stage, BP remains stable at a low level, but in another stage it

TABLE III Summary of Other Studies Evaluating the Effect of Antihypertensive Agents on Nocturnal BP

Antihypertensive Agents		Dose (mg)	Effect on Night BP	Reference
Adrenergic inhibitor:				
Central:				
	Methyldopa	125–500 TID	±	Gould, 1983[25]
	Guanfacine	1–6 QD	±/↓	Mann, 1980[26]
β-blocker (nonselective):	Oxprenolol*	240–344 TID	±	Miller-Craig, 1983[27]
	Pindolol*	10–30 BID	±	Floras, 1982[28]
		10–30 QD	±	Raferty, 1982[29]
	Propranolol LA	160–320 QD	±	Mann, 1980[30]
		10–60 QD	±	Rustin, 1983[31]
	Cardvedilol	50 QD	↓	Mayer-Sabellek, 1987[32]
(β_1-selective):	Atenolol	100–200 QD	±	Miller-Craig, 1979[33]
		50–200 QD	↓	Floras, 1979[34]
	Metoprolol	100 BID	↓	Mann, 1979[35]
	Metoprolol-SR	200 QD	±/↓	Lattuada, 1987[36]
α_1-blocker:	Prazosin	14 BID	±	Gould, 1983[37]
		4–20 BID	±	Weber, 1987†[38]
	Terazosin	0.5–20 QD	±/↓	Drayer, 1983[39]
$\alpha\beta$-blocker:	Labetalol	100–600 TID	↓	Balasubramanian, 1979[41]
		100–400 BID	±/↓	DeQuattro, 1988†[41]
Calcium antagonist:	Verapamil-SL	240 QD	↓	Novo, 1989†[42]
		240 QD-BID	↓	Cardillo, 1989†[43]
	Nifedipine	20–60 BID	↓	Gould, 1982[44]
		20–40 BID	↓	Hornung, 1983†[45]
	Nitrendipine	10–20 QD	±/↓	Mayer-Sabellek, 1988†[46]
	Diltiazem	120–180 BID	↓	Weber, 1988†[47]
ACE inhibitor:	Captopril	20–50 BID	±/↓	Meijer, 1986[48]
	Lisinopril	20 QD	↓	Herpin, 1989†[49]
	Ramipril	10–40 QD	±/↓	Heber, 1988[50]

* ISA (+) ↓ Significant, ± ns. † Indirect method
Abbreviations as in Table II.

undergoes considerable fluctuations;[8] the greatest decreases are seen in sleep-stages III and IV.[15] However, BP does not decrease unchecked during sleep; rather it has a fixed minimum limit. In other research we have designated this level "base blood pressure," and it is extremely important in determining the frequency distribution of BP during sleep.[17,18]

Among patients with mild to moderate hypertension, there is a group (L-type) whose BP falls under 110/70 mm Hg during sleep, the 2 SD upper limit value for the normotensive subjects (Fig. 3). In the present study, about one third of our patients in both the younger and older groups were L-type patients; even though their BP was high during the day, it underwent a marked decrease into the upper normotensive range during sleep (Table I, Fig. 3). This nighttime drop, seen also in W-type patients, does not imply that the reduction in nighttime blood pressure with antihypertensive agents is necessary, particularly in the older L- and W-type subgroups.

It is not yet clear what regulates this nighttime and daytime BP. Among the few reports on the hemodynamics in sleeping humans, 2 reports showed that cardiac output decreased during sleeping[19,20] and another revealed a decline in TPRI.[21] Our data showed that cardiac output decreased in the younger group, but TPRI decreased in the older group during sleep. This may be because the older group already had a low cardiac output during wakefulness, so it could not drop much further when they slept. Instead, peripheral vascular resistance dropped. This decrease in peripheral vascular resistance is probably confined to the main organs, such as the heart (myocardium), kidneys and brain, where it maintains blood circulation. In the older patients, therefore, an excessive reduction in total peripheral vascular resistance or in cardiac output induced by antihypertensive medication may cause a decrease in blood flow to the major organs. Moreover, waking BP is elevated by everyday psychosomatic activity, and the concentration of plasma catecholamines is higher during waking than during sleep. There is a proportionate increase in BP and catecholamine concentration.[22,23] Consequently, sympathetic nerve activity is considered to play a greater role in elevation of BP during wakefulness than during sleep.

The effect of antihypertensive medication on nocturnal BP is related to a variety of factors, such as the time of administration, administered dosage, number of administrations/day and duration of effect, so it is not possible to conclude definitively which of the pharmacologic characteristics of a drug plays a role. Because our laboratory has little therapeutic data, we have surveyed reports of other researchers on the effects of various antihypertensive agents on nocturnal BP and summarized our impression of their work in Table III.[25-50] As these studies did not use the same methods, we relied on our impressions of the data, indicating significant effects with downward arrows and nonsignificant effects with a ± sign. Based on a combination of these reports and the results of our study, for all of the drugs examined the reduction of BP during the night increased as the number of daily administrations was increased from once to twice and 3 times daily.

Moreover, with the same prescribed administration methods, the central-adrenergic inhibitors methyldopa and guanfacine (which we administered at bedtime) tended to produce a smaller reduction in BP during the night than during the day, probably because during the day BP is elevated by sympathetic nerve activity, which is suppressed by central-adrenergic inhibitors. Among the β blockers, those having ISA, such as oxprenolol and pindolol, have been reported to have a low antihypertensive effect during the night.[24] This may be considered attributable to the fact that β blockers, which are ISA positive, cause only a minor reduction, or even an increase, in heart rate during sleep. The α_1-blocker prazosin had little antihypertensive effect during the day or night, but thrice daily administration of bunazosin seemed to lower blood pressure at night as well as during the day. The same tendency toward lower night and daytime BP was observed for the $\alpha\beta$ blockers. The calcium antagonists, on the other hand, showed some nighttime blood pressure reduction following once-daily administrations, but they showed the greatest effect when administered 2 or 3 times/day. The ACE inhibitors may have a nighttime BP-lowering effect equal to or somewhat less than that of the calcium antagonists.

To summarize, central-adrenergic inhibitors and β blockers with ISA have a larger BP-lowering effect during waking hours and a tendency toward a somewhat smaller effect during sleep, and peripheral vasodilators show a tendency toward an increased BP-lowering effect during sleep as the number of daily administrations is increased.

In some elderly patients with pathophysiologic conditions such as reduced cardiac output and marked decreases in BP during sleep (L-type patients), it is better to avoid antihypertensive agents that cause excessive nighttime reductions in BP. The data in Tables II and III may provide a reference for antihypertensive treatment of these patients. However, since hemodynamics during sleep after antihypertensive drug administration remain undefined and observations have not yet been performed in age-matched older hypertensive patients, future research is needed to determine the optimal antihypertensive drugs and dosage regimens for elderly hypertensive patients.

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Antihypertensive Agents, Serum Lipoproteins and Glucose Metabolism

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Effective blood pressure control with traditional high-dose diuretic therapy has led to a distinct decrease in cerebrovascular morbidity and mortality, but failed to achieve a satisfactory reduction of coronary complications and sudden death. The same applies also for β blockers, although they have been shown to be effective in secondary prevention of myocardial infarction. It is suspected that conventional antihypertensive treatment has an unfavorable effect on coronary risk factors other than hypertension.

For instance, thiazide-type diuretics can impair glucose tolerance and increase the potentially atherogenic serum low-density lipoprotein (LDL) cholesterol fraction and triglycerides. Beta blockers without partial intrinsic sympathomimetic activity increase serum triglycerides and tend to lower the potentially antiatherogenic high-density lipoprotein (HDL) cholesterol. Certain β blockers may also impair glucose tolerance, particularly when they are combined with diuretics. Calcium channel blockers, angiotensin converting-enzyme inhibitors and α_1-receptor blockers do not adversely affect lipoprotein or carbohydrate profiles. The latter two drug classes may even increase insulin sensitivity, and α_1 blockers may also slightly improve lipid metabolism.

The prognostic relevance of drug-induced dyslipidemia and/or glucose intolerance awaits further clarification. In the meantime, it is of clinical interest that several of the generally available antihypertensive drugs seem to be metabolically neutral or sometimes perhaps even potentially beneficial with regard to the lipoprotein and carbohydrate metabolism.

(Am J Cardiol 1991;67:26B–35B)

Hypertension, an increase in low density lipoprotein (LDL) cholesterol or decrease in high density lipoprotein (HDL) cholesterol, and impaired glucose tolerance or diabetes mellitus often occur in association.[1-4] Moreover, these disturbances can augment the risk for coronary heart disease, angina pectoris, myocardial infarction and, as a result, congestive heart failure.[5] Similarly, elevated blood levels of triglyceride (Tg)-rich lipoproteins may be linked to coronary problems, at least in some patient groups.[5,6]

In the hypertensive population, conventional high-dose diuretic therapy, with older sympatholytics or the newer β blockers as step-2 agents and hydralazine-type vasodilators as step-3 agents, have lowered blood pressure effectively. Such therapy also improves overall cardiovascular and, in particular, cerebrovascular prognosis, but has had little beneficial effect on the course of coronary heart disease.[7] In patients with mild hypertension, high-dose diuretic monotherapy has reduced stroke but not coronary complications, whereas monotherapy with the β blocker propranolol has slightly improved both the cerebrovascular and coronary prognosis in nonsmokers, but failed to provide such benefit to smokers.[8] The latter result underscores the adverse effects of smoking.[5] Conventional antihypertensive therapy may unfavorably influence coronary risk factors other than high blood pressure. Interactions with cardiac hypertrophy,[9] serum electrolytes, angiotensin II, catecholamines, clotting factors, and lipoprotein and glucose metabolism are under particular consideration. The present review will discuss the effects of antihypertensive drugs on two of these risk factors: lipoprotein and glucose metabolism.

EFFECTS OF ANTIHYPERTENSIVE DRUGS ON LIPOPROTEINS

Thiazide-type or loop diuretics: Thiazide-type diuretics, administered as a monotherapeutic regimen, tend to increase serum total cholesterol by an average of 4%, serum LDL cholesterol by an average of 10% (Fig. 1), as well as very low-density lipoprotein (VLDL) cholesterol.[10-32] HDL cholesterol (Fig. 1) and its major apoproteins, Apo-A_1 and -A_2, are largely unchanged. Thus, the LDL/HDL cholesterol and total/HDL cholesterol ratios are frequently elevated. Loop diuretics, such as furosemide—and the structurally related mefruside, piretanide and muzolimine—also cause an increase in these

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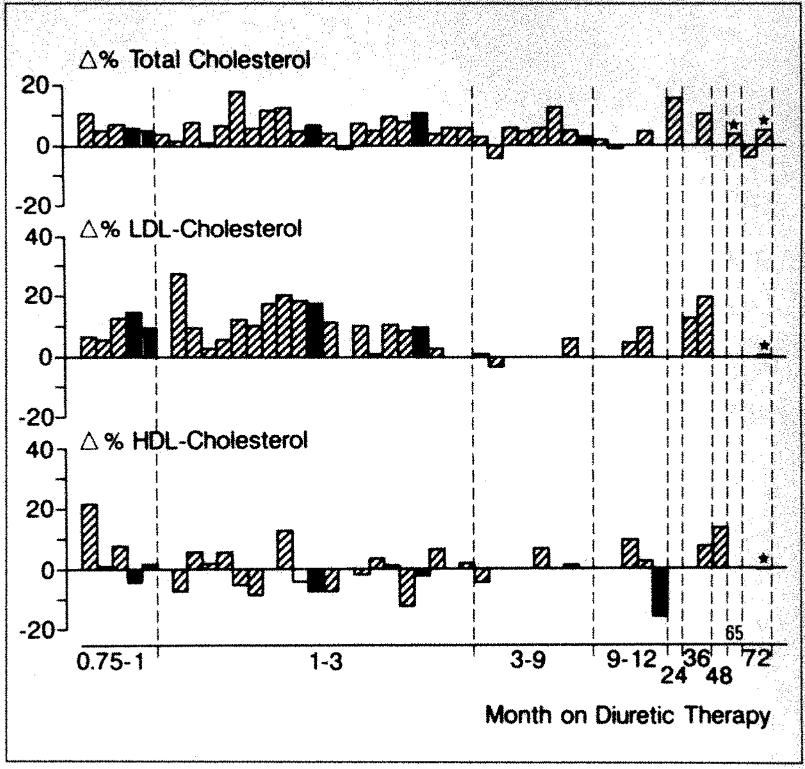

FIGURE 1. Percentage changes in serum lipoprotein-cholesterol fractions as related to the duration of a therapy with thiazide-type (hatched bars) or certain loop diuretics (closed bars). n ≥ 10 subjects per study. Asterisks denote differences between study groups on diuretics as compared with study groups on no diuretics or no antihypertensive drugs.

ratios.[15,30,31] Moreover, slight increases in VLDL-Tg and/or total Tg (average +9%) were noted in most, but not all, studies with thiazide-type or loop diuretics.

A critical aspect of any metabolic side effect is its course over time. Diuretic-induced dyslipidemia persists for at least 1 year, with some studies documenting changes up to 6 years (Fig. 1). In the Multiple Risk Factor Intervention Trial (MRFIT),[25] a reduction in total cholesterol in a group receiving no diuretics was distinctly blunted by thiazide-type diuretics, even after 5 to 6 years of this monotherapy (Fig. 2). Similar results were found in the Hypertension Detection and Follow-up Program (Fig. 3).[27]

The mechanisms of diuretic-induced dyslipidemia, although unclear, may involve both increased synthesis and decreased catabolism. Diuretics slightly increase sympathetic nervous activity[30] and levels of circulating norepinephrine. This may, in turn, promote lipolysis[33] as well as stimulating hepatic synthesis of cholesterol subsequently secreted as VLDL. Atherogenic serum cholesterol may indeed depend on noradrenergic modulation, as suggested by significant positive correlations between plasma norepinephrine and LDL plus VLDL cholesterol, before and after sympathetic neuron blockade in patients with essential hypertension or renal failure.[34] Thiazide-type and loop diuretics can also impair insulin sensitivity,[35] which alone or together with the resulting compensatory hyperinsulinemia can promote hypertriglyceridemia, increase LDL cholesterol, a tendency toward decrease HDL cholesterol, and atherogenesis.[36,37]

In women, interactions between diuretics and lipoproteins seems to depend on the menopausal state. In postmenopausal women, chlorthalidone produced changes in total and LDL cholesterol similar to those in men; no changes were seen in premenopausal women,[38] indicating a "protective" influence of the premenopausal state. It seems that estrogens increase the number of hepatic LDL binding sites and stimulate the hepatic uptake of chylomicron remnants.[39]

The development of dyslipidemia may also be linked to the type and dose of the administered diuretic. Indapamide, in the usual antihypertensive dose of 2.5 mg/d, does not produce dyslipidemia.[40] (Note that the methyl-substituted isoindoline portion of indapamide differentiates this agent structurally from chlorthalidone, hydrochlorothiazide, furosemide and ticrynafen.[30]) Compared with the rather low effective antihypertensive dose of indapamide,[41] unnecessarily high daily doses of chlorthalidone, hydrochlorothiazide (50 to 100 mg/d) or other thiazides were utilized in studies focusing on interactions with lipoproteins as well as in the large therapeutic programs in hypertensive patients.

Since effects of thiazides on serum potassium, glucose tolerance and uric acid are dose-dependent, in low doses they may also be less prone to modify lipoprotein metabolism. Thus far, studies of this aspect have produced contradictory results. One report suggested that a higher thiazide dose is associated with greater lipid abnormalities, but 3 other studies could not confirm this result.[28,30,42,43]

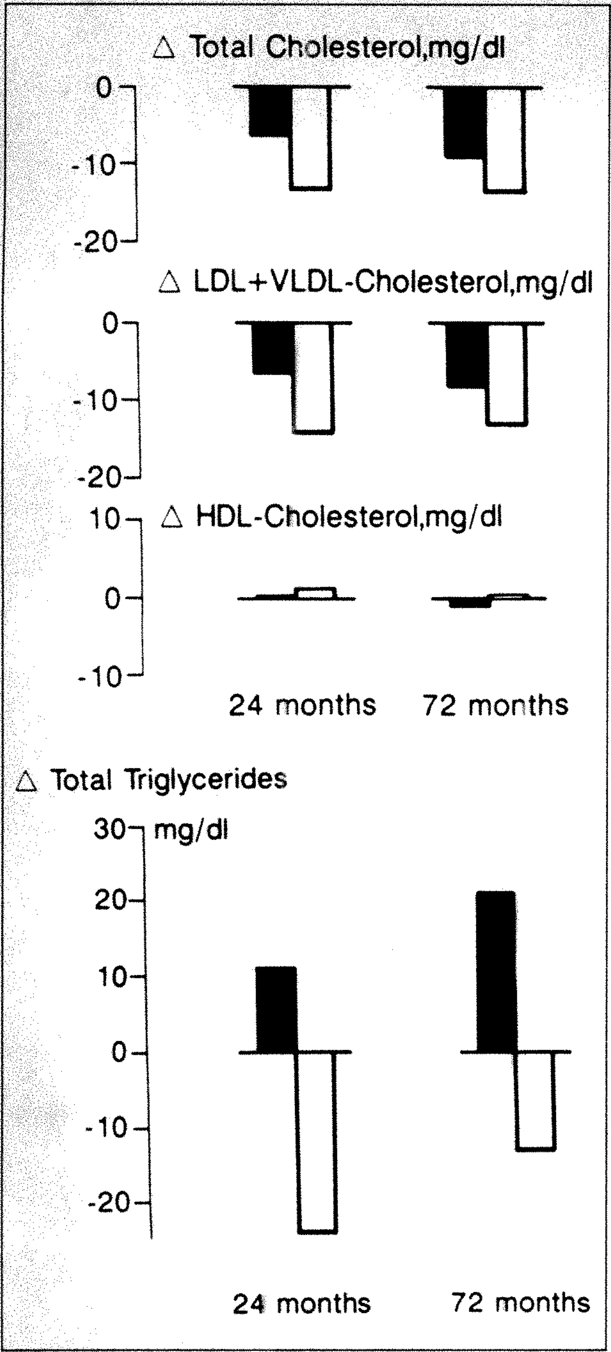

FIGURE 2. Absolute changes from baseline in total serum cholesterol, sum of LDL-cholesterol and VLDL-cholesterol, and HDL-cholesterol *(top)* and in total triglycerides in men in the MRFIT after 24 and 72 months of follow-up *(bottom)*. All patients were on diet. Open bars represent patients without diuretics, closed bars patients with diuretic therapy (based on ref. 25).

Beta blockers: Beta blockers, administered as monotherapy,[18,22,24,26,28–30,44–66] generally do not modify serum total and LDL cholesterol levels (Figs. 4 and 5). However, some β blockers can increase total or VLDL-Tg and decrease HDL cholesterol (Figs. 4–6). In the usual clinical antihypertensive doses, unselective β blockers without intrinsic sympathomimetic activity (ISA), such as propranolol, sotalol or timolol, tend to cause the most pronounced changes, increasing total serum Tg by an average of 29% and decreasing HDL cholesterol by 7% (Fig. 6). These alterations are slightly less pronounced with highly selective β_1 blockers without ISA, such as atenolol, metoprolol or betaxolol (Tg, +18%; HDL cholesterol, −7%), and even more discrete with β blockers with mild ISA, such as oxprenolol, acebutolol, mepindolol or bopindolol (Tg, +13%; HDL cholesterol, −2%). Pindolol, with more prominent ISA, generally does not modify Tg and may even increase HDL cholesterol. This action resembles the stimulatory influence of the β receptor agonist terbutaline on HDL cholesterol.[67] Finally, celiprolol, a β_1-selective blocker with ISA and additional β_2-stimulating as well as α_2-blocking properties, even tended to lower Tg and distinctly elevated HDL cholesterol. This potentially interesting profile needs further investigation. Variations in serum Tg and HDL cholesterol levels were similarly pronounced from 1 month and up to ≥ 3 years of β-blocker monotherapy (Figs. 4 and 5). Observations on celiprolol are limited to 1 year.

The mechanisms by which β adrenergic blocking drugs exert their effects on lipoprotein metabolism are only partly understood. Beta blockade is accompanied by increased α-adrenergic tone. Alpha-adrenergic tone is known to lower lipoprotein lipase (LPL) activity,[68] which results in increased Tg levels due to an impaired catabolism of Tg-rich lipoproteins. Thus HDL, which depends on VLDL catabolism, decreases, as indicated by a close inverse relationship between β-blocker induced changes in total Tg and HDL cholesterol. Nonselective blockers apparently inhibit LPL activity more than β_1 selective blockers. Certain β blockers also tend to reduce insulin sensitivity,[69] which lowers LPL activity and the removal of Tg from the circulation. Pindolol can increase lecithin cholesterol acyltransferase (LCAT) activity, thereby elevating HDL cholesterol by suppressing the HDL-LCAT cycle.[70]

Other sympatholytics: Reserpine, methyldopa, debrisoquine, urapidil, clonidine and the α-β blocker labetalol do not adversely modify the serum lipoproteins.[24,30] Postsynaptic α_1 blockers (e.g., prazosin, doxazosin, terazosin) decrease total Tg and cholesterol, and slightly increase HDL cholesterol (Fig. 7).[32,49,56,58,71–77] This potentially beneficial effect can be attributed to an increase in LPL,[30] which contrasts with the decrease induced by β blockers described above. Moreover, α_1 blockers may promote cholesterol catabolism through increased LDL-receptor activity and by raised levels of cyclic adenosine monophosphate secondary to inhibition of phosphodiesterase activity.[78,79]

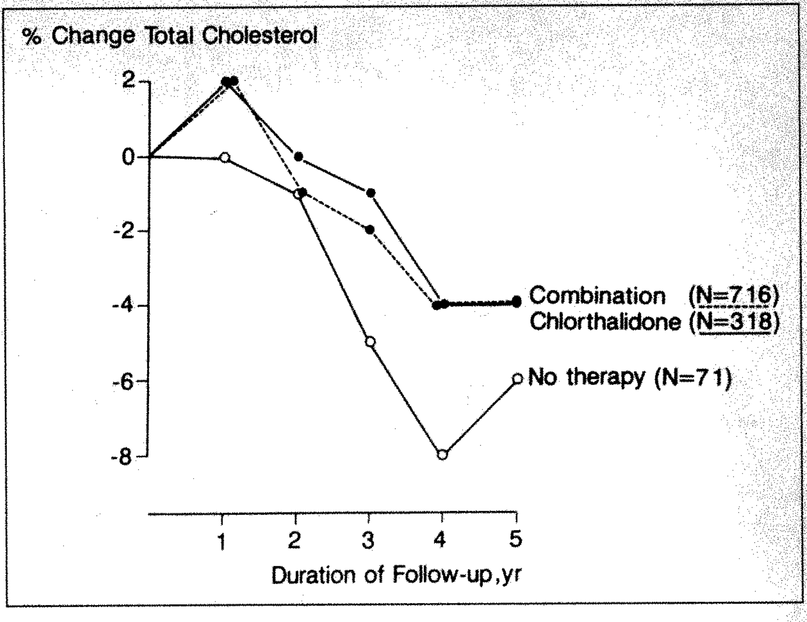

FIGURE 3. Percentage change from baseline in total cholesterol of cohorts of patients on chlorthalidone therapy, combination therapy or no therapy, after a follow-up of at least 5 years in the Hypertension Detection and Follow-up Program. (based on ref. 27).

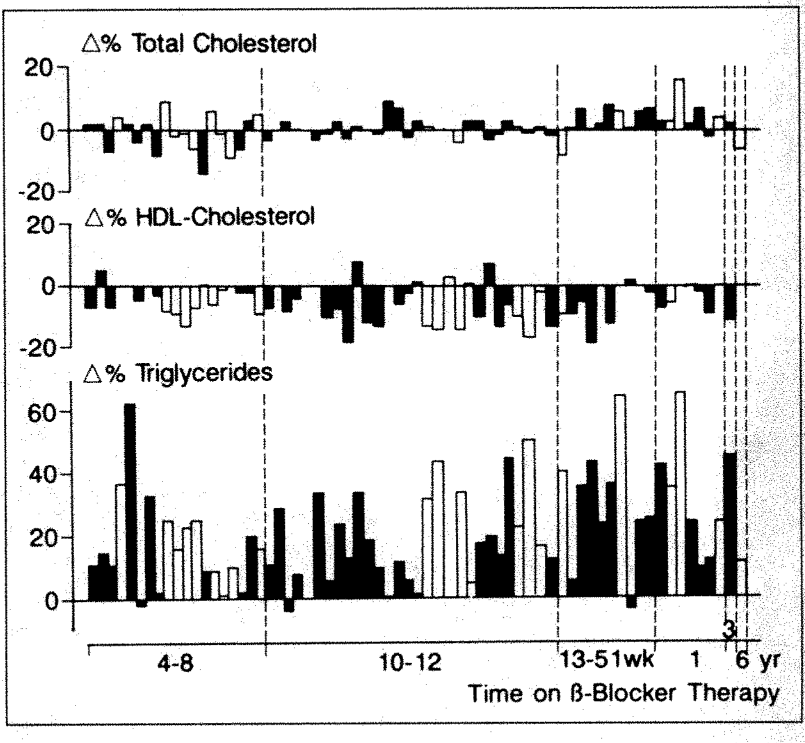

FIGURE 4. Percentage change in total serum cholesterol and HDL-cholesterol and serum triglycerides in relation to the duration of monotherapy with different β blockers without intrinsic sympathomimetic activity. n ≥ 10 subjects per study. Open bars represent nonselective β blockers; closed bars represent selective β₁ blockers).

Combination of sympatholytics with diuretics: Diuretic-induced increases in LDL-cholesterol were prevented or reversed by short-term concomitant administration of certain β blockers,[30,80] but not by concomitant sympatholytics, such as reserpine or methyldopa.[24,30] In combined diuretic-prazosin treatment, slightly higher HDL-cholesterol was reported.[24,30]

Angiotensin converting enzyme (ACE) inhibitors and calcium antagonists: ACE inhibitors (eg, captopril, enalapril and quinapril)[30,35,81-84] and calcium antagonists (eg, verapamil, nifedipine, nitrendipine, diltiazem etc.)[30,73,85-87] do not seem to exert undesirable effects on serum lipoproteins (Figs. 8-10).

HYPERTENSION, INSULIN AND LIPOPROTEINS

Hypertension has a high prevalence among states characterized by decreased insulin sensitivity or hyperinsulinemia such as obesity, impaired glucose tolerance, non-insulin-dependent diabetes mellitus. Moreover,

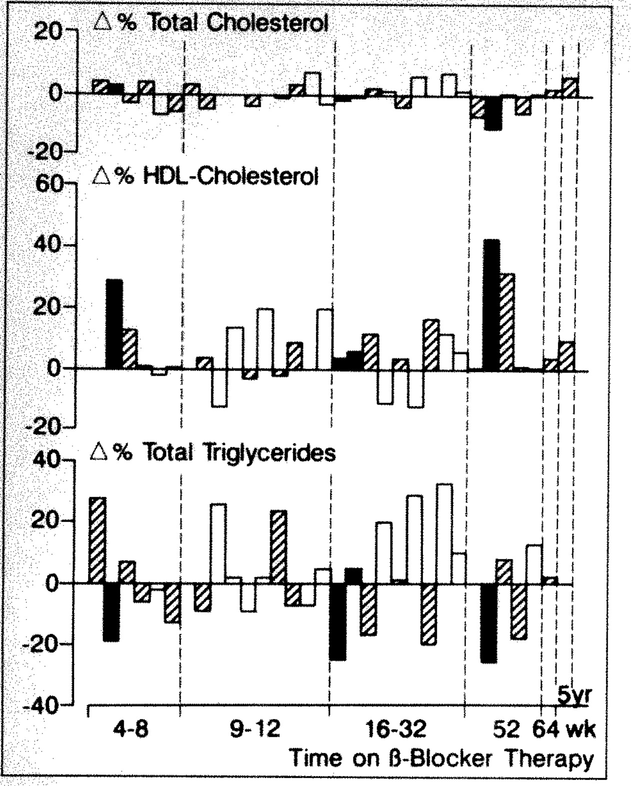

FIGURE 5. Percentage change in total serum cholesterol and HDL-cholesterol and serum triglycerides in relation to the duration of a monotherapy with different β blockers with intrinsic sympathomimetic activity (ISA). n ≥ 10 subjects per study. Hatched bars represent pindolol, closed bars celiprolol, and open bars the effects of other β blockers with ISA.

there is evidence that, even in the absence of obesity or diabetes mellitus, essential hypertension may be associated with insulin resistance, which elicits a compensatory increase in insulin secretion.^{1,3,37} Hyperinsulinemia may increase intracellular calcium concentration^{36,88} promote proliferation of vascular smooth muscle cells^{89} and intracellular cholesterol accumulation^{90} and at least acutely, enhance renal sodium reabsorption^{91} and sympathetic nervous system activity.^{92} One or more of these mechanisms may contribute to the genesis of essential, obesity-associated and diabetes-associated hypertension, as well as promote dyslipidemia.

The interaction of insulin with the lipid metabolism may elevate serum Tg and LDL cholesterol, decrease HDL cholesterol levels^{3,36,93} and cause an increase in adipose tissue, particularly in the presence of excess amounts of glucose. The alterations in circulating lipids seem to result at least in part from an impairment of insulin's inhibitory influence on hepatic VLDL secretion and stimulatory action on LPL.^{94} On the other hand, growth factors—insulin in particular—promote LDL-receptor-mediated uptake of cholesterol and reduce HDL-receptor activity, thus impairing cholesterol efflux

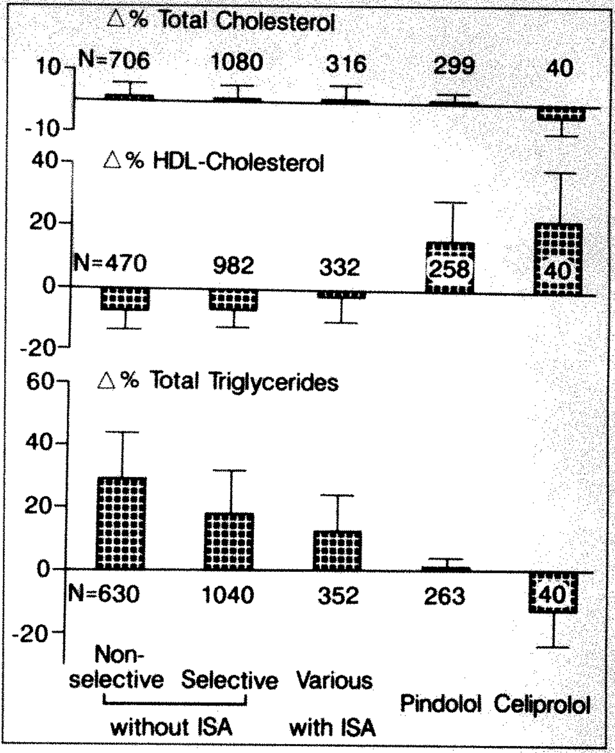

FIGURE 6. Mean percentage response of total serum cholesterol, HDL-cholesterol and total triglycerides to monotherapy with different β blockers (mean ± SD). n ≥ 10 subjects per study. Numbers denote the total numbers of reported cases.

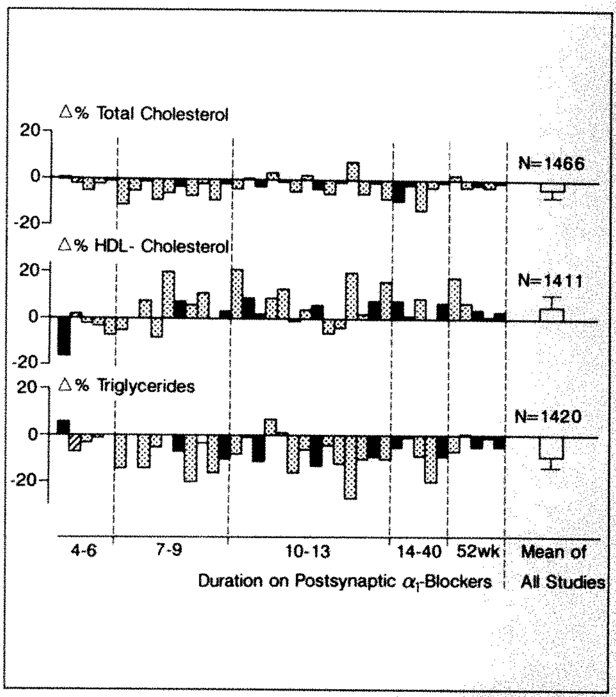

FIGURE 7. Percentage change in total serum cholesterol and HDL-cholesterol and serum triglycerides in relation to the duration of a monotherapy with postsynaptic α_1 blockers. Dotted bars represent prazosin; closed bars, doxazosin; hatched bars, terazosin. n ≥ 10 subjects per study. Average changes in all reported subjects given as mean ± SD.

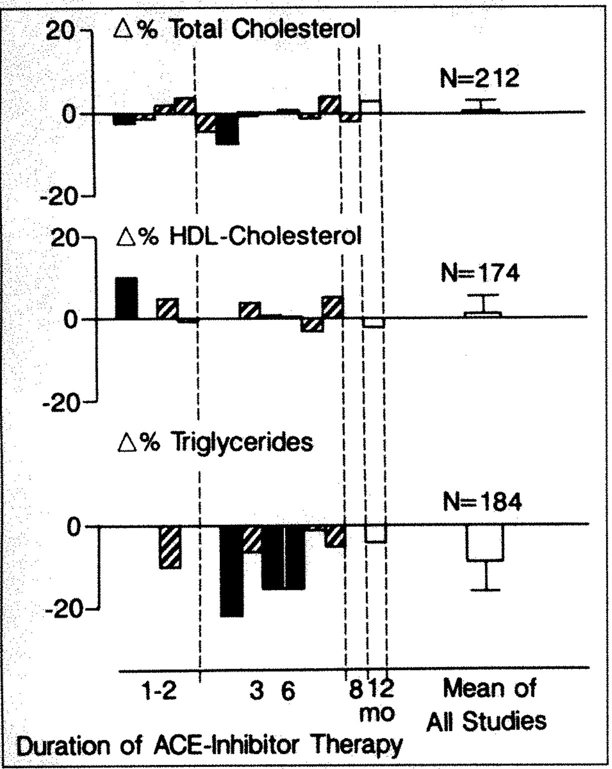

FIGURE 8. Percentage change in total serum cholesterol and HDL-cholesterol and serum triglycerides in relation to the duration of a monotherapy with ACE inhibitors. Hatched bars represent captopril; closed bars, enalapril and open bars, other ACE inhibitors. n ≥ 15 subjects per study. Average changes in all reported subjects given as mean ± SD.

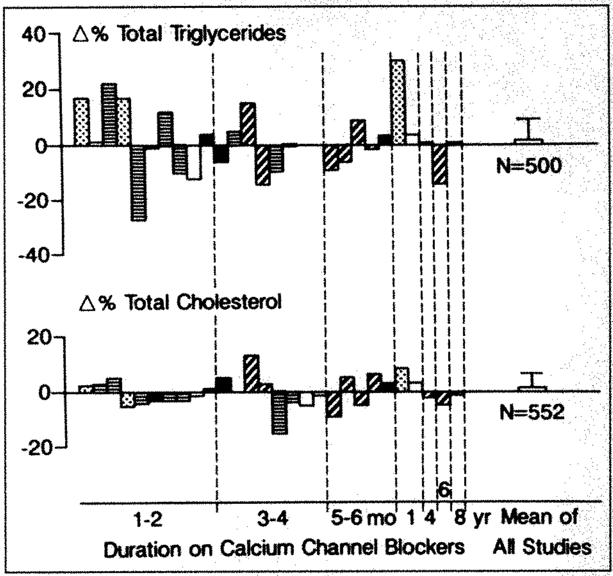

FIGURE 9. Percentage change in total serum triglycerides and total cholesterol in relation to the duration of monotherapy with different calcium antagonists. Hatched bars represent verapamil; closed bars, diltiazem; dotted bars, nitrendipine; horizontal lined bars, nifedipine; and open bars, other calcium antagonists. n ≥ 10 subjects per study. Average changes in all reported subjects given as mean ± SD.

from macrophages and vascular smooth muscle cells, which in turn results in intracellular accumulation of cholesteryl esters.[90] Insulin may also enhance the Tg content in the aorta, increase aortic intimal thickness[89,95] and stimulate the growth and migration of vascular smooth muscle cells from the media through the lamina elastica interna into the subintimal space. This complex metabolic disturbance, which could be complemented by hyperinsulinemia-induced alterations in clotting,[96] is potently atherogenic.[36,90] In fact, the blood level of insulin has been found to correlate independently with the risk of developing coronary artery disease.[97,98]

It is evident from this that drugs that decrease insulin sensitivity or elevate plasma insulin during fasting or after glucose load also exert a potentially adverse influence on lipid metabolism, cellular proliferation and cardiovascular regulation.

EFFECTS OF ANTIHYPERTENSIVE DRUGS ON GLUCOSE METABOLISM

Thiazide diuretics can precipitate hyperglycemia in both non-diabetic and diabetic patients, particularly in the postprandial state.[99,100] This disturbance probably results from decreased insulin sensitivity[35,101] and impaired insulin secretion[102] (Table I). The adverse effects of thiazides on carbohydrate metabolism are dose-dependent, persist during long-term treatment[103] and may be, at least in part, reversible after discontinuation of such therapy.[99]

Some β blockers can also interfere with carbohydrate metabolism. The cardioselective β_1 blockers atenolol[69,106] or metoprolol[69] decrease insulin sensitivity, at least during short-term treatment (Table I). Moreover, in animals[107] and humans,[108] administration of the nonselective β blocker propranolol inhibited insulin secretion, whereas the β-selective blockers practolol[107] or metoprolol[108] did not.

Figure 11 illustrates changes in glucose metabolism after long-term therapy with diuretics and/or β blockers in some antihypertensive treatment trials. In the Medical Research Council (MRC) Trial on mild hypertension, impaired glucose tolerance was present after 5 years of treatment in 7.8% of patients on bendrofluazide (10 mg/d) as compared with 2.2% on placebo.[104] In the Oslo Study,[105] fasting blood glucose levels after 5 years of treatment were only minimally higher in the patient group receiving hydrochlorothiazide (50 mg/d) than in the placebo group. In the Veterans Administration (VA) study[21] and the studies of Berglund et al.[19] and Lewis et al.,[99] which were not placebo-controlled, increases in fasting blood glucose after 1 to 6 years of thiazide treatment ranged from 2.5 to 13%, as compared with values at the start of therapy. Certain observations suggested

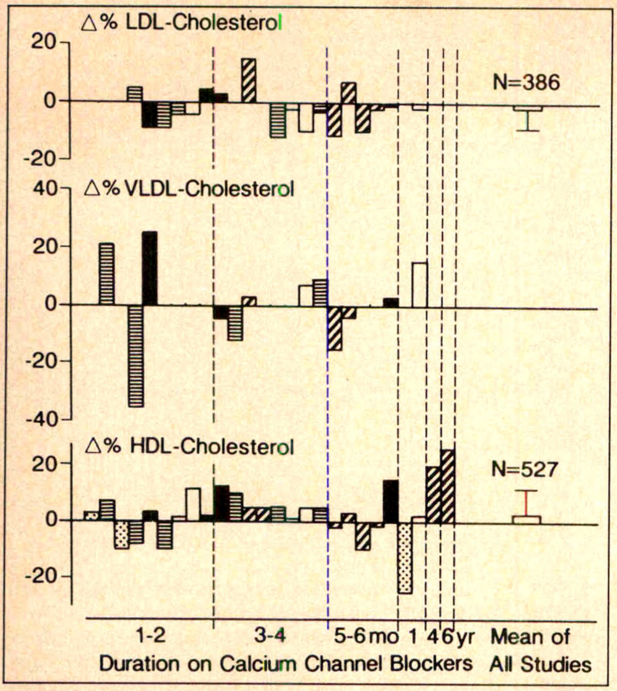

FIGURE 10. Percentage change in serum cholesterol fractions in relation to the duration of monotherapy with different calcium antagonists. Hatched bars represent verapamil; closed bars, diltiazem; dotted bars, nitrendipine; horizontal lined bars, nifedipine; and open bars, other calcium antagonists. n ≥ 10 subjects per study. Average changes in all reported subjects given as mean ± SD.

TABLE I Effects of Antihypertensive Agents on Glucose Tolerance, Insulin Metabolism and Insulin Sensitivity in Humans

		Insulin		
	Glucose Tolerance	Plasma Levels	Secretion	Sensitivity
Diuretics				
Thiazide-diuretics	↓↓	↑	= or ↓	↓
Loop diuretics	↓	?	↓	?
Potassium-sparing diuretics	↓	?	?	?
β-Blockers				
Unselective	= or ↓	?	↓	↓
β_1-selective	= or ↓	↑	=	↓
ACE-inhibitors	↑	↓	?	↑
Calcium channel blockers				
Dihydropyridine-type	=	=	? (↓)	↓
Diltiazem	=	↓	? (↓)	↑
Postsynaptic α1-Blockers	↑	↓	↑	↑

Decrease: ↓ = modest, ↓↓ = of clinical relevance. Increase: ↑ = modest.

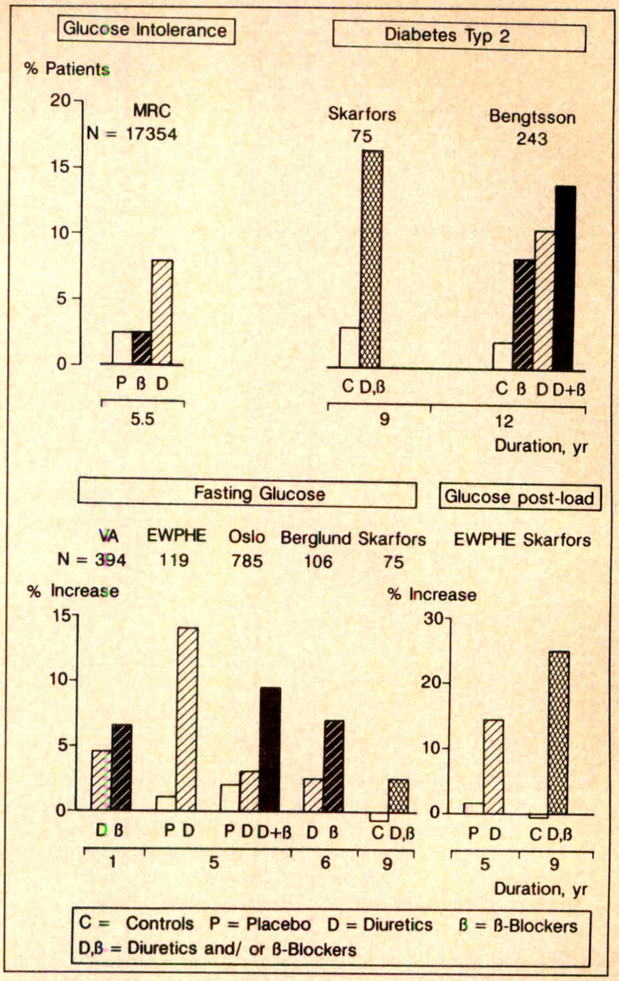

FIGURE 11. Percentage changes in fasting and post-load blood glucose levels and percentage of patients developing glucose intolerance or diabetes mellitus type 2 in some long-term antihypertensive trials, with diuretics and/or beta blockers.

that loop-type diuretics[109,110] and potassium-sparing diuretics[111] may have less pronounced effects on glycemic control than do thiazides. Nevertheless, in the European Working Party on Hypertension in the Elderly (EWPHE),[112] fasting blood glucose after 1 year of treatment was 12% higher in patients receiving a thiazide/potassium-sparing diuretic combination (hydrochlorothiazide, 25 to 50 mg/d, and triamterene, 50 to 100 mg/d) than in the placebo group; glucose levels during glucose tolerance testing were elevated by 12% (compared with placebo) in the diuretic treated group (Fig. 11). However, the diuretic agent indapamide, given in the normal anti-hypertensive dose of 2.5 mg/d, does not seem to impair glucose tolerance.[41] Age, glycemic control at the start of treatment and perhaps the type of diuretic may also influence the metabolic interaction of diuretics.

Concerning β blockers, the MRC trial[104] revealed no difference in the number of patients developing glucose intolerance on propranolol as compared with placebo (Fig. 11). However, in the VA study[21] and the study of Berglund et al.,[19] fasting blood glucose levels tended to rise more on propranolol than on thiazide therapy. Bengtsson et al.[113] observed a remarkable increase in the incidence of diabetes mellitus type 2 during therapy with different β blockers as compared with placebo. Finally, alterations in blood glucose appeared to be most pronounced when β blockers were administered in combination with diuretics.[105,113,114]

ACE inhibitors do not seem to influence the carbohydrate metabolism adversely.[30] Glycemic control even improved in some studies,[30,35,115,116] and increased insulin sensitivity was reported after short-term treatment with captopril in some hypertensive patients (Table I).[30,35,115,116]

With few exceptions,[117,118] calcium antagonists in usual clinical doses have no apparent adverse influence on carbohydrate metabolism.[119,120] Insulin sensitivity was unaltered following 24 weeks of therapy with diltiazem[106] (Table I). Short-term administration of the dihydropyridine-type calcium antagonist amlodipine in 38 normotensive subjects did also not modify insulin sensitivity or plasma insulin levels.[121]

Similarly, sympatholytic agents other than the β blockers generally have no undesirable influence on carbohydrate metabolism.[122–124] The postsynaptic α_1 blocker prazosin was even reported to improve insulin sensitivity in obese hypertensive patients.[124]

RELEVANCE AND OUTLOOK

Whether the lipoprotein changes induced by certain antihypertensive drugs can modify the long-term prognosis of patients is still unclear. In patients with high plasma cholesterol levels (pre-treatment cholesterol >6.5 m*M*/liter), long-term cholesterol lowering with either diet or drugs produced a 1.5% decrease in coronary heart disease for every 1% reduction in cholesterol. Whether this correlation also holds for both increases or decreases in cholesterol from initially normal or mildly elevated serum levels is not yet known. Therefore, attempts to calculate a potential impact of diuretic-induced increases in total serum cholesterol and LDL cholesterol on coronary prognosis would be largely speculative.

Impaired glucose tolerance, resistance to insulin-mediated cellular glucose uptake and hyperinsulinemia are cardiovascular risk correlates. Thus, impairment in insulin sensitivity or alteration in insulin release induced by certain antihypertensive or other drugs represents an undesirable side effect.

Diuretic therapy may concomitantly aggravate several potential cardiac risk factors, through insufficient prevention or regression of left ventricular hypertrophy, electrolyte imbalance and sympathetic and angiotensin II-stimulation. Although it has been difficult to demonstrate a primary preventive effect of β blockers on coronary prognosis, such agents have been found to be effective in at least the secondary prevention of myocardial infarction. It follows that diuretics and β blockers have done at least "some good"; the prognostic efficacy of newer drug classes, such as calcium antagonists, ACE inhibitors and postsynaptic α_1 blockers remains to be demonstrated. Thus, possible differential indications for the various antihypertensive drugs are only beginning to emerge. Still, at this stage, it is of clinical relevance that several of the generally available antihypertensive drugs seem to be metabolically "neutral" or even potentially beneficial with regard to the lipoprotein and glucose metabolism.

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Editor's note: Each bar in Figs. 1, 4, 5 and 7–10 represents data from a separate study. These have not been individually referenced due to pressure of space. Most of these studies can be found in reference 30.

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Bopindolol: Czechoslovak Experience With a New Beta Blocker in the Treatment of Hypertension

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Bopindolol is a nonselective β blocker with mild intrinsic sympathomimetic activity. One of the drug's main benefits is its prolonged effect, lasting for 24 hours, which makes it possible to administer bopindolol in a single daily dose, a fact that may improve patient adherence to therapy. A double-blind study was performed in two centers, comparing bopindolol with metoprolol in 86 hypertensive patients. Baseline diastolic blood pressure (BP) was 100 to 120 mm Hg. The effects of bopindolol or metoprolol on BP and heart rate were similar: return to normal values was achieved in 70% of patients with either drug. A 6-month study at another center found that bopindolol did not affect the levels of total cholesterol, low-density and high-density lipoprotein cholesterol or triglycerides. Another 12-month study documented a decrease in total cholesterol, apolipoprotein (apo) A1 and apo B. The apo A/B ratio rose, thus improving the atherosclerotic index. No deterioration of glucose tolerance or immunoreactive insulin response to glucose was seen after 6 months of bopindolol administration. Bopindolol satisfactorily modifies not only resting but also exercise BP during isometric and isotonic load, thus reducing BP fluctuation during physical activities of the hypertensive patient. The drug exerts no effect on renal and liver function, electrolyte balance and hematologic parameters. Bopindolol is a very useful drug of first choice in mild and moderate hypertension. Bopindolol's main advantages include its prolonged action, good tolerance and a beneficial effect on risk factors of atherosclerosis (lipid and carbohydrate metabolism).

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Beta blockers are one of the main groups of drugs used in the treatment of hypertension. Beta blockers meet all requirements for long-term ambulatory treatment of hypertension.[1] In monotherapy, they reliably control blood pressure (BP) in 40% to 50% of patients. While lowering systolic and diastolic BP at rest and during exercise, they do not produce postural hypotension. The frequency of undesirable effects is low, usually not exceeding 10%. A disadvantage of nonselective and cardioselective β blockers is their unfavorable metabolic action; they have an adverse effect on lipid and carbohydrate metabolism.[2] The increase in triglycerides is often substantial and may reach 20% to 30% compared with the initial level;[3] high-density lipoprotein (HDL)-cholesterol decreases by 5% to 10%.

The impact of antihypertensive drug therapy on ischemic heart disease is less marked than has been expected.[4] A possible explanation is the unfavorable effect of antihypertensive therapy on lipoprotein and carbohydrate metabolism. Beta blockers with intrinsic sympathomimetic activity (ISA) do not exert this unfavorable effect on HDL-cholesterol levels.[1,5-7] That is why this group of β blockers is currently receiving special attention.

Bopindolol, which has been tested in the treatment of hypertension in several centers in Czechoslovakia, is a very potent β-adrenoceptor-blocking drug with moderate ISA and long duration of action.[8,9] In clinical pharmacologic studies, equivalent cardiac β-adrenoceptor blockade was reached with 1 mg bopindolol, 100 mg atenolol or 10 mg pindolol.[8] The relatively slow onset of action of bopindolol may be at least partly responsible for its good tolerability.

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BOPINDOLOL VERSUS METOPROLOL: A DOUBLE-BLIND STUDY

A double-blind study comparing bopindolol with metoprolol in the treatment of essential hypertension has been performed in two centers in Czechoslovakia (Widimský and Lefflerová in Prague, and Lupínek in Brno).[10]

Criteria for inclusion were as follows: (1) essential hypertension with a diastolic BP of 100 to 120 mm Hg; (2) age between 18 and 70 years for either sex; (3) absence of previous undesirable effects of β blockers; and (4) withdrawal of previous antihypertensive drugs.

Exclusion criteria were: (1) secondary forms of hypertension; (2) malignant or accelerated hypertension; (3) cerebrovascular or hypertensive encephalopathy within the past year; (4) history of heart failure or myocardial infarction; (5) severe metabolic disease; and (6) contraindication to β-blocker therapy. The study included 86 hypertensive patients; 44 patients were assigned to a group treated with bopindolol, and 42 subjects to a metoprolol group. Duration of hypertension did not differ significantly in either group. Statistical analysis showed that both groups were homogeneous and did not differ in any of the parameters studied (Table I).

Patients were withdrawn from all drugs administered previously and were provided placebo for 2 weeks (dose A). In case inclusion criteria were met, patients in the respective groups were administered dose B (1 mg bopindolol once daily or 50 mg metoprolol twice daily) (Table II). If on the next follow-up visit, diastolic BP was 95 mm Hg or more, dose C (2 mg bopindolol once daily or 100 mg metoprolol twice daily) was given. If even this dose failed to control BP effectively, dose D (3 mg bopindolol once daily or 150 mg metoprolol twice daily) was administered (Table II). Patients had their BP measured with a sphygmomanometer in the supine and upright positions after 3 minutes of rest, with heart rate determined simultaneously. Patients were followed in the same manner at 4-week intervals for 3 months.

During the placebo phase and after 3 months of effective therapy, the following laboratory tests were performed: electrocardiogram, ASAT, ALAT, blood count, urea, creatinine, bilirubin, potassium, cholesterol, uric acid, plasma glucose and urinalysis.

Results were analyzed using BMDP programs.[11] Comparison of parameters among groups was performed using the two-sample Student's *t* test. To assess real-time changes in the parameters studied, analysis of variance with repeated measures and one grouping factor was used.

Our results (Tables III and IV) have shown that both drugs are effective in controlling both systolic and diastolic BP in supine as well as in standing positions. We did not find any difference in the antihypertensive efficacy of the two drugs. Both drugs decreased heart rate in the supine and standing positions.[10]

TABLE I Characteristics of Examined Group of Patients Treated With Bopindolol or Metoprolol

		Bopindolol	Metoprolol
Total no.		44	42
Men		23	23
Women		21	19
Age (yrs)		50 ± 10	51 ± 11
Duration of hypertension (yrs)		7	5
WHO stage of	I	27	25
	II	16	15
	III	1	2

WHO = World Health Organization.

TABLE II Dosage Protocol Used in the Double-Blind Study Comparing Bopindolol With Metoprolol

Dose	Bopindolol	Metoprolol
A	Placebo 2 × daily	Placebo 2 × daily
B	1 mg in the morning + placebo in the evening	50 mg 2 × daily
C	2 mg in the morning + placebo in the evening	100 mg 2 × daily
D	3 mg in the morning + placebo in the evening	150 mg 2 × daily

The doses employed in the 79 patients who completed the bopindolol study were as follows: 22 patients were provided 1 mg once daily, 11 subjects 2 mg once daily, and 9 patients received 3 mg once daily. The group treated with metoprolol included 20 patients who received 50 mg twice daily, 11 patients with 100 mg twice daily and 6 receiving 150 mg twice daily.

Values for blood count, bilirubin, ASAT, ALAT, creatinine and urea were within the normal range in all patients before and after therapy. Values of cholesterol, glucose and uric acid were not changed at the end of 3 months of therapy with either drug.

Adverse effects: The study was not completed by 7 patients (2 treated with bopindolol and 5 receiving metoprolol). However, 2 patients in the metoprolol group discontinued therapy for subjective reasons within the placebo period. During active therapy, undesirable side effects—weakness, fatigue, bradycardia or sweating—were the reason for discontinuing therapy in 2 patients receiving metoprolol and 1 patient receiving bopindolol. In 1 patient a dose as high as 150 mg of metoprolol twice daily failed to decrease diastolic BP below 115 mm Hg.

In another 2 patients, therapy was discontinued because of concomitant disease: one patient receiving metoprolol was excluded from the study for acute non-Q-wave myocardial infarction; another treated with bopindolol was excluded for acute pancreatitis. The remaining 79

TABLE III Blood Pressure and Heart Rate During 3-Month Therapy With Bopindolol and Metoprolol (Supine Position)

	Placebo			1st Month			2nd Month			3rd Month		
BP Supine	BPs	BPd	HR	BPs	BPd	HR	BPs	BPd	HR	BPs	BPd	HR
Bopindolol	154	102	75	143	89	67	140	87	68	142	90	67
(n = 44)	±16	±7	±9	±16	±10	±8	±13	±7	±7	±13	±7	±7
Metoprolol	157	103	73	149	91	67	143	90	66	145	90	66
(n = 42)	±13	±6	±10	±22	±12	±9	±17	±10	±10	±17	±9	±8

All values of systolic and diastolic blood pressure and heart rate were significantly influenced by metoprolol or bopindolol ($p < 0.01$). No significant difference between the effect of metoprolol and bopindolol was observed.
SBP = systolic blood pressure (mm Hg); DBP = diastolic blood pressure (mm Hg); HR = heart rate (beats/min).

TABLE IV Blood Pressure and Heart Rate During 3-Month Therapy With Bopindolol and Metoprolol (Standing Position)

	Placebo			1st Month			2nd Month			3rd Month		
BP Standing	BPs	BPd	HR	BPs	BPd	HR	BPs	BPd	HR	BPs	BPd	HR
Bopindolol	151	104	80	143	93	71	142	91	71	143	93	71
(n = 44)	±16	±6	±9	±15	±10	±9	±15	±8	±8	±16	±8	±7
Metoprolol	155	106	78	149	94	71	146	94	69	147	93	69
(n = 42)	±16	±7	±10	±19	±11	±9	±19	±10	±10	±19	±9	±8

All values of systolic and diastolic blood pressure and heart rate were significantly influenced by metoprolol or bopindolol ($p < 0.01$). No significant difference between the effect of metoprolol and bopindolol was observed.
SBP = systolic blood pressure (mm Hg); DBP = diastolic blood pressure (mm Hg); HR = heart rate (beats/min).

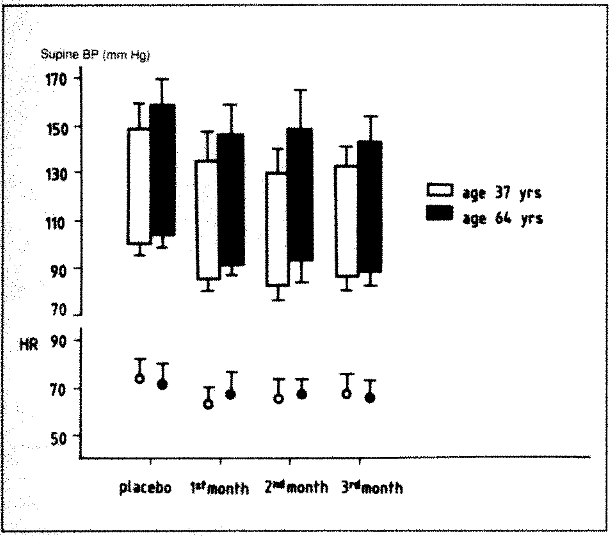


FIGURE 1. Bopindolol in the treatment of hypertension in the elderly in the supine position. BP = blood pressure; HR = heart rate.

patients tolerated therapy very well and did not complain of undesirable side effects.

Our results confirm the very good antihypertensive effect of bopindolol in patients with mild and moderate hypertension.[8,12,13] Compared with metoprolol, bopindolol is equally effective in controlling both systolic and diastolic BP. Using β-blocker monotherapy, normalization of diastolic BP (<95 mm Hg) was attained in 70% of our patients with mild and moderate hypertension.

Bopindolol in the treatment of the elderly hypertensives: Age did not influence the antihypertensive efficacy of β blockers. Bopindolol or metoprolol induced absolute or relative blood pressure reductions similar in the younger (30–40) and older (60–69) age groups (Fig. 1).

These data indicate that the antihypertensive efficacy of β blockers is not age-related. Our findings are in agreement with previous data by Weidmann and Bousquet et al[13,14] but differ from those of Bühler et al[15] and Hulthen et al.[16] According to Bühler et al, the antihypertensive effect of β blockers is least manifest in patients aged 60 to 69 years.[15] About 80% of patients over 60 years of age in the above study did not respond to β blockers with a sufficient decrease in BP. In our study, however, normalization was reached in 80% of elderly patients with mild hypertension (Fig. 2).

Effect of bopindolol treatment on handgrip BP values in hypertensive subjects: In an open study, Dvorăk tested the effect of bopindolol on BP values both at rest and during handgrip in 15 patients with mild hypertension. Mean age was 46.2 years (range, 37–60); 10 subjects were men and 5 were women. The handgrip test was performed after 2 weeks of placebo treatment and after 1, 2 and 3 months of treatment with bopindolol at a dose of 1 to 2 mg daily.

A significant decrease in BP both at rest and during handgrip could be observed after the first month of bopindolol treatment (Fig. 3).

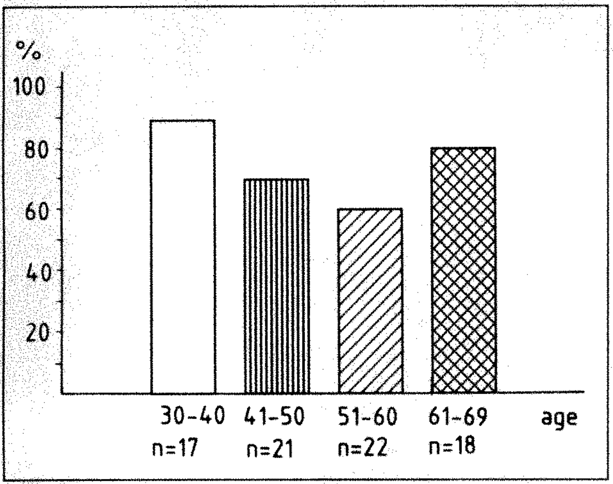


FIGURE 2. Beta blockers (bopindolol or metoprolol) in the treatment of elderly hypertensives: percentage of hypertensive patients in whom monotherapy with β blockers led to diastolic blood pressure lower than 95 mm Hg.

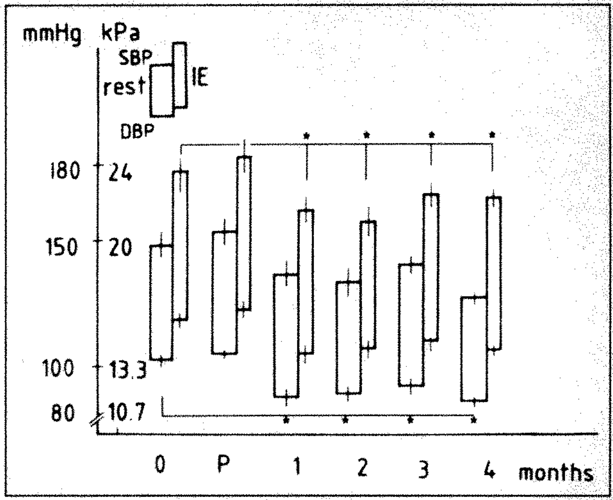


FIGURE 3. The effect of bopindolol treatment on blood pressure values at rest and during isometric exercise (handgrip) in hypertensive subjects. SBP = systolic blood pressure; DBP = diastolic blood pressure; rest. = resting values; IE = isometric exercise (handgrip).

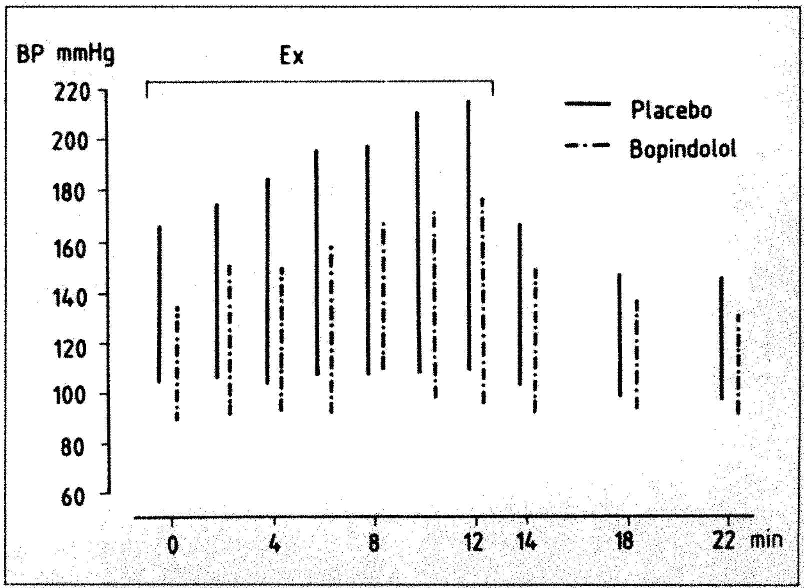
During placebo treatment, 75% of patients with mild hypertension had a pathologic BP response to the handgrip test, i.e., systolic BP ≥180 mm Hg or diastolic BP ≥125 mm Hg. After 3 months of therapy with bopindolol, only 26% of patients showed a pathologic response to the handgrip test (p <0.001).

Effect of bopindolol on BP during exercise: A study was conducted of BP values before and after 3 months of bopindolol treatment at rest and during exercise in 8 subjects in an open study (O. Mayer, Plzeň). Mean age of the patients was 51.6 years (range, 18 to 64). All patients had mild or moderate hypertension. After 2 weeks of placebo phase, bopindolol treatment was started and continued for 10 weeks. A submaximal exercise test was performed at the end of the placebo phase and again after 10 weeks of bopindolol treatment.

The researchers used the bicycle ergometer test with 3 loads without interruption, each lasting 4 minutes. Exercise tests were performed in the sitting position. Exercise systolic and diastolic BP decreased significantly during bopindolol treatment (Fig. 4).

Effect of bopindolol on lipids in hypertensive subjects: The effect of bopindolol on lipids was studied in an open 12-month study including 19 subjects in one center.[17] Mean age was 46.2 years (range, 17 to 66). The patients' body weight remained unchanged throughout the study. At entry, the patients were asked to stop their

FIGURE 4. The effect of bopindolol treatment on blood pressure values during exercise in hypertensive subjects. BP = blood pressure; Ex = exercise.



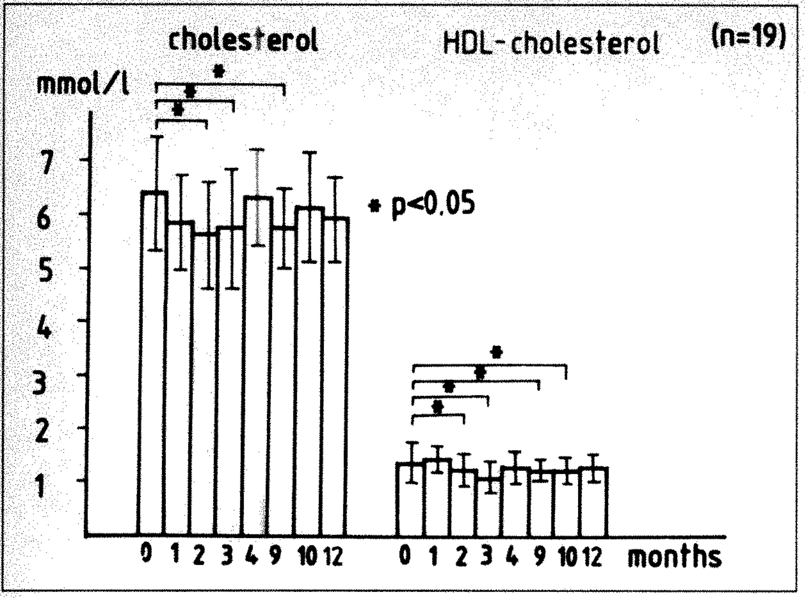


FIGURE 5. Cholesterol and HDL-cholesterol values during the treatment of hypertension with bopindolol.

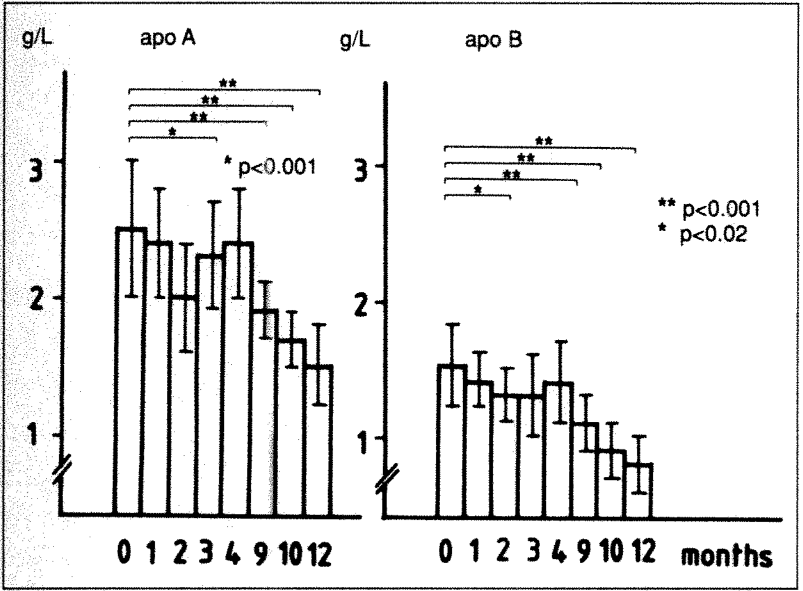


FIGURE 6. Apolipoprotein values in hypertensive subjects during treatment with bopindolol.

current antihypertensive therapy and were provided with placebo for 2 weeks. After completion of the placebo phase, bopindolol was administered for a total period of 12 months.

At the end of the placebo period and then once a month, total cholesterol, HDL-cholesterol, triglycerides and apo A and B were determined.

A comparison of initial values with values after 12 months of therapy revealed no statistically significant differences in total cholesterol, HDL-cholesterol or triglyceride levels or in the total cholesterol/HDL-cholesterol ratio. The ratio did not decrease in 1 year of treatment, and hence the atherogenic index did not deteriorate (Fig. 5).

TABLE V Bopindolol Treatment and Lipids

	Placebo	1st Month	3rd Month	6th Month
Total cholesterol	5.84 ± 0.47	5.34 ± 0.20	5.71 ± 0.31	5.71 ± 0.31
HDL-cholesterol	1.42 ± 0.16	1.62 ± 0.27	1.69 ± 0.17	1.68 ± 0.15
Triglycerides	2.01 ± 0.38	2.21 ± 0.27	1.88 ± 0.32	1.88 ± 0.32
APO A1	1.62 ± 0.08	1.66 ± 0.06	1.65 ± 0.07	1.65 ± 0.07
APO B	1.85 ± 0.09	0.98 ± 0.09	0.86 ± 0.08	0.86 ± 0.07

No significant differences were found; (n = 10).
APO = apolipoprotein; HDL = high-density lipoprotein.

Compared with placebo values, the serum concentrations of apo A and B after 12 months of therapy decreased significantly (p <0.001) (Fig. 6). The apo A/B

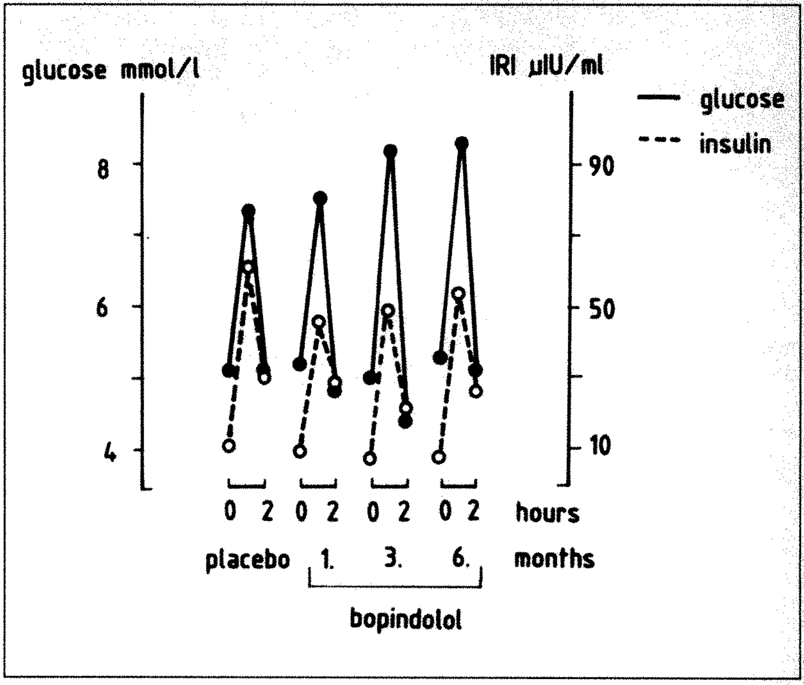


FIGURE 7. Plasma glucose and insulin values before and after 75 g oral glucose in hypertensive subjects during bopindolol treatment.

ratio rose markedly, from 1.61 during the placebo phase to 1.79 after 12 months of treatment with bopindolol, indicating an improved atherogenic index.

Effect of bopindolol treatment on carbohydrate metabolism: The effect of bopindolol on carbohydrate and lipid metabolism was studied in 10 hypertensive patients in an open 6-month study.[18] No significant changes in total cholesterol, low-density lipid cholesterol and very low-density lipid cholesterol were observed (Table V).

Blood glucose did not change significantly. During the glucose tolerance test, glycemia decreased 120 minutes after glucose load below initial values during bopindolol treatment when compared to the placebo phase (Fig. 7). Immunoreactive insulin values remained the same both before and after the oral glucose test during bopindolol treatment.

Our results are thus in agreement with previous data demonstrating that bopindolol does not have an adverse effect on metabolic risk factors of coronary artery disease.[6,7]

In conclusion, our results show that bopindolol is a potent antihypertensive drug able to normalize BP in 70% of hypertensive patients. It is very well tolerated; the incidence of undesirable effects is low and may be even lower than with placebo.[13] Its long duration of action enables administration of a single dose in the morning. It is known that one third of hypertensive patients do not comply with therapeutic recommendations. Once-daily administration may have a favorable effect on patient adherence to therapy.[19] Bopindolol does not influence lipid and carbohydrate metabolism; therefore it is well indicated in hypertensive patients with hyperlipoproteinemia or diabetes mellitus.

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Review of State-of-the-Art Beta-Blocker Therapy

Lennart Hansson, MD

Beta-adrenoceptor blocking drugs have been used in the treatment of hypertension for more than 2 decades. During this time they have reached the position of first-line therapy for hypertension and are recommended as such by the Joint National Committee (U.S.A.) in 1988 and by the World Health Organization/International Society of Hypertension in 1983 and 1989. This is because of the favorable relationship between the antihypertensive efficacy of these drugs and the rate and severity of their adverse effects. Of particular interest is the possibility that β blockers may protect against coronary artery disease (CAD). With regard to secondary prevention against CAD, statistically highly significant and clinically relevant reductions of mortality and the risk of reinfarction have been shown in prospective, double-blind, placebo-controlled trials. A primary preventive effect against CAD, on the other hand, has only been shown in open trials without placebo control. However, in spite of the lack of clear proof, this effect still appears to be a logical possibility. Some new findings with β blockers appear to be of particular interest: beta blockade may reduce myocardial necrosis in patients with marked elevations of plasma catecholamines due to traumatic head injury; a similar protective effect in other situations of severe stress, e.g., acute myocardial infarction, would be of great clinical value. Experimental studies also suggest that β blockers may have antiatherosclerotic effect in animals fed an atherogenic diet and subjected to stress. Again, clinical confirmation of such results would be of great significance.

(Am J Cardiol 1991;67:43B–46B)

Treatment of arterial hypertension constitutes a large and important part of all medical care provided in industrialized nations today. Over the years, several groups of antihypertensive compounds have become available clinically, one of which is the β-adrenoceptor blocking compounds, commonly referred to as β blockers. These agents were introduced for the treatment of hypertension some 20 years ago and have rapidly reached the status of first-line treatment, which they still hold.

This brief review will cover some of the issues of β-blocker treatment that are currently of clinical interest as well as some new aspects whose clinical importance may increase in the future.

BETA BLOCKERS

Beta blockers have been used in the treatment of hypertension for well over 2 decades. They were accepted as first-line treatment in many centers in the early 1970s and this position has been strengthened in many ways since then, e.g., by official recommendations such as the one by the World Health Organization/International Society of Hypertension (WHO/ISH) in 1983.[1] That β blockers still are regarded as first-line treatment by influential expert committees is exemplified by the recommendations of the Joint National Committee (U.S.A.) in 1988[2] and by the recent guidelines for the management of mild hypertension issued by WHO/ISH in 1989.[3]

Ahlquist first presented the concept of β-adrenoceptors in 1948.[4] He divided the adrenoceptors into the subtypes α and β, defining the β-receptor by its sensitivity to stimulation with agonists in the following order: isoprenaline > epinephrine > norepinephrine.[4] Later Lands et al[5] carried this definition one step further by subdividing β-adrenoceptors into the subtypes β_1 and β_2. The β_1-adrenoceptors have an equal affinity for norepinephrine and epinephrine, whereas the β_2-adrenoceptors have a greater affinity for epinephrine than norepinephrine.[5]

Ten years after Ahlquist's definition of the adrenoceptors, pharmacologic blockade of β-adrenoceptors was made possible through the use of dichloroisoprenaline.[6]

James W. Black (the 1988 Nobel Laureate in Medicine and Physiology) is the inventor of several of the important pharmacologic compounds that have the ability to block β-adrenoceptors, e.g., pronethalol and pro-

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TABLE I Pharmacologic Properties of Some Beta-Adrenoceptor Blocking Agents

Compound	Blocks β_1	Blocks β_2	MSA	β_1-ISA	β_2-ISA	Antihypertensive	Remarks
Propranolol	+	+	+	–	–	+	
Timolol	+	+	–	–	–	+	
Oxprenolol	+	+	+	+	+	+	
Pindolol	+	+	–	–	+	+	
Atenolol	+	–	–	–	–	+	
Practolol	+	–	–	+	+	+	
Epanolol	+	–	–	+	–	?	
ICI 118,551	–	+	?	–	–	–	
Labetalol	+	+	+	–	–	+	α-blockade

ISA = intrinsic sympathomimetic activity; MSA = membrane-stabilizing activity (usually not clinically important at normal dosage).

TABLE II Withdrawal of Randomized Treatment Due to Adverse Effects in Male Patients in the Medical Research Council (MRC) Trial of Treatment in Mild Hypertension (Rate/1,000 Patient Years)

Patient Years	Bendroflumethiazide (2,452)	Propranolol (2,738)	Placebo (6,776)
Impaired glucose tolerance	9.4	3.7	2.5
Gout or serum urate >501 μmol/L	12.2	2.6	1.0
Impotence	19.6	5.5	0.9
Raynaud's phenomenon	0	5.5	0.2
Skin disorder	0.4	2.2	0.2
Dyspnea	0	8.0	0.2
Constipation	1.6	0.4	0
Lethargy	6.9	10.2	0.3
Nausea, dizziness, headaches, etc.	8.6	6.7	1.2

(Adapted from the Medical Research Working Party.[27])

pranolol. In 1964, the first clinical reports dealing with the antihypertensive effect of these compounds were published.[7-9] In particular, Prichard's work[8-10] was very important for the rapid development in this area, and he and his group published many of the major early papers dealing with the antihypertensive efficacy of β blockers. Other large-scale studies soon confirmed these initial positive results.[11-13]

Antihypertensive mode of action: Numerous mechanisms have been proposed in attempts to explain how β blockers lower elevated arterial pressure. Obviously, the blockade of β_1-adrenoceptors appears to be one important component, since both nonselective blockers (β_1 and β_2) and β_1-selective agents reduce blood pressure, whereas β_2-selective blockers do not lower blood pressure.[14]

In addition, β blockers with intrinsic sympathomimetic activity (ISA), such as pindolol and bopindolol, are of particular interest since they lower blood pressure via a slightly different mechanism than β blockers without ISA. The common β blockers cause an acute fall in cardiac output with a concomitant increase in total peripheral resistance (TPR), and consequently blood pressure does not change acutely.[15,16] During continued treatment with such agents, cardiac output remains at a reduced level, but in responding patients, blood pressure falls, owing to a decrease in TPR.[15,16] In contrast, β blockers with marked ISA do not reduce cardiac output and do reduce TPR, leading to an acute fall in blood pressure that is maintained during chronic treatment.[17]

The underlying mechanisms behind these rather clear-cut hemodynamic alterations are perhaps a bit more controversial. The importance of a β blocker-induced decrease in renin release has been debated. Today it appears that most investigators question the importance of plasma renin both as a predictor of response and as a major mechanism by which blood pressure is affected. This issue has been discussed in depth in the recent excellent textbook Beta-Blockers in Clinical Practice.[18]

In addition to the importance of ISA, particularly ISA affecting β_2-adrenoceptors (briefly reviewed above), there are other ancillary properties, e.g., the membrane-stabilizing effect, which, however, does not seem to be important for the antihypertensive effect[19] (Table I).

In this context one should stress the dissociation between the onset of β-adrenoceptor blockade and the antihypertensive effect. Beta blockade can be demonstrated within minutes after the intravenous administration of a β blocker, whereas the antihypertensive effect occurs gradually over hours or days.[20] The dissociation in time between these two effects also can be observed upon cessation of treatment, when blood pressure only gradually returns to the initial level whereas heart rate increases much more rapidly.[21]

Antihypertensive efficacy: Some of the early investigators, including Prichard, reported that the antihypertensive efficacy of propranolol was equal to that seen with α-methyldopa, bethanidine or guanethidine.[10] In formal comparisons, β blockers have been shown to be as potent as diuretics,[22] and various β blockers usually also are found to possess similar antihypertensive efficacy.[23,24]

In combination with dihydropyridine-derived calcium antagonists such as isradipine or felodipine, β blockers may cause a marked antihypertensive effect.[25,26]

Side effects: The side effects caused by β blockers are in general well known, and are exemplified by the adverse effects reported in the large prospective intervention trial in mild hypertension conducted by the Medical Research Council in the United Kingdom[27] (Table II). (The side effects of the β_1-selective agent practolol, which was withdrawn from oral clinical use more than a decade ago, appear to be peculiar to this compound and will not be dealt with here.)

A certain debate has centered around central nervous system side effects, e.g., vivid dreams and sleep disturbance. Some investigators have found a higher incidence of such complaints in patients receiving treatment with lipid-soluble β blockers, whereas others have found little or no difference between water-soluble and lipid-soluble agents. This topic is reviewed in somewhat greater detail in the new edition of the Handbook of Hypertension.[28]

Another important topic is the extent of the potentially negative metabolic effects that β blockers may exert. An extensive review by van Brummelen, comprising 22 studies in this area, showed that β blockers with marked ISA caused the smallest changes in the lipid profile.[29]

Prevention of coronary heart disease: Since coronary artery disease (CAD) is the major complication of hypertension, it is understandable that much interest has been devoted to the ability of antihypertensive agents to prevent this common and serious condition. In secondary preventive studies (i.e., studies in which β blockers have been given to patients who have already suffered a myocardial infarction), the preventive effect has been established beyond doubt. A meta-analysis of 25 such trials, conducted with several different β blockers, found that β blockers caused a highly significant 22% reduction in mortality and an equally significant 27% reduction in the reinfarction rate compared to placebo.[30]

Unfortunately, the primary preventive effect against CAD, i.e., prevention of myocardial infarcts in patients who have previously not suffered this complication, is much less clear-cut. A primary preventive effect has been predicted by many authors for several years, but so far placebo-controlled intervention trials in hypertensives have failed to demonstrate this highly desirable effect. It must therefore be concluded that although a primary preventive effect against CAD appears logical when β blockers are used in the treatment of hypertension, definitive proof is still lacking.

TABLE III Pharmacologic Properties of Some Newer Beta-Adrenoceptor Blocking Agents

Compound	Distinguishing Features
Adimolol	Beta$_1$-selective, long plasma half-life, long duration of action
Bisoprolol	Beta$_1$-selective, high degree of selectivity
Bopindolol	Nonselective, ISA, very long duration of action
Carvedilol	Nonselective, vasodilating due to α blockade
Celiprolol	Beta$_1$-selective, vasodilating due to β_2-agonism and other mechanisms
Dilevalol	Nonselective, vasodilating mainly due to marked β_2-agonism

ISA = intrinsic sympathomimetic activity, i.e., β-adrenoceptor agonism.

Recent developments: A number of new β blocking agents are being produced, some of which are still in clinical trials (Table III). It is worth noting that some of these new agents, in addition to their β-blocking ability, have other properties of potential clinical importance, such as ISA or prolonged duration of action. This is a desirable development, since it gives the prescribing physician the possibility of selecting an agent within the β-blocker group which is particularly suitable for the individual patient.

Antiatherosclerotic effect: Most of the cardiovascular complications in hypertension are associated with or directly due to atherosclerosis. Against this background, it is interesting to note that a review of 13 experimental animal studies shows that administration of β blockers had a retarding effect on the development of atherosclerosis in 10 of these studies.[31] In particular, the results obtained in cholesterol-fed monkeys subjected to psychosocial stress show that β blockade significantly reduced coronary atherosclerosis.[31] When and if such results can be confirmed in clinical trials, it is obvious that they would be of major clinical importance.

Cardioprotection: A number of pharmacological compounds, including β blockers, have been shown to reduce the size of myocardial necrosis in animals subjected to experimental ligation of a coronary artery. Of more immediate clinical interest are studies comparing prospective, double-blind administration of a β blocker or placebo to patients under severe stress due to traumatic head injuries.[32] These patients showed marked elevations of plasma catecholamines, directly correlated to increased levels of CK-MB, sometimes to levels indicative of myocardial infarction.[32] This rise in catecholamine and CK-MB levels was completely prevented by β-blocker treatment. At autopsy no patients in the β-blocker group showed signs of myocardial necrosis, whereas clear necrotic lesions were identified in the few hearts available for examination in the placebo group.[32] Such results point to the interesting possibility that treatment with β blockers could prevent myocardial damage in situations characterized by severe stress and marked elevations of plasma catecholamines. Again, such an effect would be of great potential clinical importance.

CONCLUSIONS

Beta blockers are still first-line drugs for the treatment of arterial hypertension. They are effective and well tolerated and also less expensive than some of the newer classes of compounds currently available. In addition, their secondary preventive effect against CAD is proven beyond doubt, and it is still logical and realistic to expect a primary preventive effect against CAD.

The antiatherosclerotic effect and the prevention of myocardial necrosis shown by β blockers in some recent studies can justify expectations of future clinical advantages. Furthermore, new and improved β blockers are likely to contribute to the important role that β blockers play and will continue to play in the treatment of hypertension for many years to come.

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Clinical Experience With Bopindolol: Summary of Poster Presentations

Masaharu Ikeda, MD, and Yoshiyuki Nakashima, MD

Updated, comprehensive theories on the mechanisms and clinical benefits of β blockers in general were advanced in the oral presentations and panel discussions of this symposium. The topics of the poster presentations focused on the clinical characteristics and usefulness of bopindolol, a new β-adrenoceptor blocking agent, on hypertension and angina pectoris, based on clinical experience.

Bopindolol is a prodrug that is a potent β-adrenoceptor antagonist with an extremely long duration of action. Pharmacologic experiments have revealed that bopindolol blocks both β_1- and β_2-adrenoceptors as well as having intrinsic sympathomimetic activity (ISA).

Hemodynamic characteristics of bopindolol: Tsukiyama et al investigated the hemodynamic effects of bopindolol compared with atenolol (a cardioselective β blocker with no ISA) by radiocardiography using iodine-131-labeled serum albumin. The study protocol was a crossover design, with treatment with the first drug for a period of 6 weeks before crossover to the other drug for another 6 weeks. At the end of each period, hemodynamic and clinical examinations were performed. During the atenolol treatment period, heart rate was reduced and cardiac output tended to decrease, with no significant change in peripheral resistance. During bopindolol, however, there was no change in heart rate and cardiac output, with a tendency toward reduction in peripheral resistance. From these results it was concluded that the ISA of bopindolol may both counteract the increase in peripheral resistance induced by vascular β_2 blockade and also minimize the decrease in heart rate and cardiac output.

Brandao et al reported on a double-blind study employing echocardiographic evaluation of left ventricular function following 8 weeks of administration of bopindolol or atenolol in 35 patients with essential hypertension. Although the two drugs showed equal efficacy in reducing blood pressure, bopindolol reduced blood pressure by decreasing total peripheral resistance by 10.6% with no myocardial functional changes due to ISA, whereas atenolol decreased blood pressure by reduction of cardiac output by 9.7%.

These hemodynamic studies indicate that the underlying mechanisms of blood pressure reduction are different with bopindolol and atenolol and that bopindolol has a more favorable hemodynamic profile than atenolol.

Antihypertensive effects: Nakashima et al reported on the clinical efficacy of bopindolol compared with atenolol in patients with mild to moderate hypertension. The multicenter study was performed using a double-blind, parallel-group design with a placebo run-in. A total of 244 patients with essential hypertension (World Health Organization grades I, II) were treated for 12 weeks with either 1 mg bopindolol (122 cases) or 50 mg atenolol (122 cases), using a double-dummy method, after a 4-week placebo phase. Either drug significantly lowered blood pressure. The response rates were 61% for bopindolol and 65% for atenolol. Although heart rate was reduced with each drug, final values were significantly higher in the bopindolol group than in the atenolol group ($p < 0.05$). Adverse effects were minimal with bopindolol. The researchers concluded that 1 mg bopindolol once daily or 50 mg atenolol once daily controlled blood pressure with equal efficacy, but that bopindolol was a safer drug when adverse effects were considered.

Rogowski et al reported the results of once-daily bopindolol on circadian blood pressure profiles in hypertensive patients. Ambulatory blood pressure profiles were recorded in 10 patients before and after 2 weeks of treatment with 1 to 2 mg bopindolol once daily. With bopindolol, the 24-hour mean systolic blood pressure decreased from 143.7 to 127.6 mm Hg and the diastolic blood pressure from 99.4 to 88.8 mm Hg. Heart rate was reduced by 6.5 beats/min.

All hourly mean systolic and diastolic blood pressure values were reduced, with no change in the circadian pattern. No adverse events were reported during bopindolol therapy. These data suggest that 1 to 2 mg bopindolol once daily exhibits good antihypertensive efficacy during the whole 24-hour period and, by reducing awakening blood pressure, may have a beneficial antihypertensive effect.

Matsuura et al reported on the antihypertensive efficacy and safety of long-term (more than 6 months)

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administration of bopindolol, as well as on its effect on the eye. Bopindolol was given once daily at a dose of 0.5 to 2.0 mg for 6 to 12 months in 19 patients with mild to moderate essential hypertension. Ophthalmologic tests were conducted at 6 and 12 months. Bopindolol showed stable long-term antihypertensive efficacy; the response rate was 71.4%. No ophthalmologic changes were seen.

Kasahara et al performed the standing test and cold pressor test on patients receiving combined therapy with a calcium antagonist and bopindolol, to investigate the effect of stress on changes in blood pressure and plasma catecholamines.

Bopindolol was administered for 8 to 12 weeks to 11 patients with essential hypertension whose blood pressure was not reduced by calcium antagonists. Blood pressure was lowered within 2 weeks and was maintained for the duration of the combined therapy period. Following combined therapy, blood pressure and heart rate were reduced and plasma norepinephrine levels were decreased at all times compared with monotherapy, on both standing and cold pressor tests. The researchers concluded that combined therapy with a calcium antagonist and bopindolol was effective and favorable even under stress.

Cristal et al reported a field study performed in primary care clinics. They examined the dose efficacy of bopindolol and its influence on quality of life, and the efficiency of primary care clinics in evaluation of new antihypertensive drugs. Blood pressure was normalized in 68% of the patients who received 1 mg or less of bopindolol, and no significant side effects were observed. The mean score of "life satisfaction" was not affected by treatment, although one problem in the study was a dropout rate of approximately 20%. This study design also demonstrated the advantages and disadvantages of primary care clinics in drug-evaluation studies.

Welzel et al reported a comparison of the antihypertensive efficacy and patient tolerance of different daily dosages of bopindolol (0.05, 0.5, 1 or 2 mg) and nifedipine (20 mg twice daily) in a randomized, double-blind clinical trial. Of 159 patients who completed an 8-week dose titration period and a 16-week observation period, blood pressure was normalized in 94% of patients on bopindolol and in 91% of patients on 20 mg nifedipine twice daily. Patient tolerance was good with either drug, and only 3 out of 162 patients on bopindolol and 3 out of 41 patients on nifedipine discontinued because of intolerable side effects. In the final evaluation of tolerance, bopindolol was assessed to be significantly better than nifedipine ($p < 0.05$). In 135 elderly patients (≥55 years), "quality of life" was assessed by a self-administered questionnaire. An improvement in quality of life was observed in all treatment groups. The effect of nifedipine on quality of life was similar to the effect of 1 to 2 mg bopindolol. It was concluded that bopindolol and nifedipine exhibit a similar antihypertensive efficacy and a comparable positive influence on quality of life in elderly patients. However, the tolerance of bopindolol was better in patients of all ages.

Effect on atherogenic factors: Tamachi et al evaluated the effect on lipid metabolism in 66 patients with mild to moderate essential hypertension randomly allocated to 16 weeks of treatment with bopindolol or atenolol. At the end of the treatment period, 61.8% of patients in the bopindolol group and 63.3% in the atenolol group showed a sufficient reduction in blood pressure. In the bopindolol group, there were no changes in serum lipid levels throughout the treatment period; however, there were transient increases in lecithin: cholesterol acyltransferase (LCAT) activity, apolipoprotein (Apo) A C-III and total cholesterol/Apo B ratio, and transient decreases in free fatty acid, Apo B and Apo B/Apo A-I ratio were observed. In the atenolol group, transient increases in low-density lipoprotein cholesterol and Apo A-I were observed.

These findings suggest that bopindolol is as effective and well tolerated as atenolol for the treatment of hypertension, and may also even have a desirable effect on lipid metabolism.

Fitscha et al studied the effects of bopindolol on platelet function in 10 male hypertensive patients given 1 mg bopindolol/day for 8 weeks. Bopindolol significantly decreased the bicycle exercise-induced increase in platelet aggregation. During bopindolol treatment, both the slope and height of the platelet aggregation response curve were moderately decreased at rest before exercise and significantly decreased at rest after exercise. Furthermore, bopindolol significantly increased the exercise-induced decrease in platelet sensitivity to prostacyclin and prostaglandin D_2 (PGD_2). Bopindolol also significantly decreased the exercise-induced elevation in serum and plasma thromboxane (Tx) B_2. Platelet count and plasma levels of 6-keto-$PGF_{1\alpha}$, β-thromboglobulin and platelet factor 4 were not affected by bopindolol.

Fitscha et al concluded that bopindolol favorably affects platelet function in that, at therapeutic doses, it lowers exercise-induced platelet aggregation and TxB_2 formation by increasing platelet sensitivity to antiaggregatory prostaglandins. Treatment of hypertension with an agent that lowers blood pressure and inhibits platelet activation may be a clinically beneficial regimen for hypertensive patients.

Effect on kidney and heart: One of the objectives of antihypertensive therapy is to reverse core organ (brain, heart and kidney) abnormalities with the goal of at least preserving their blood flow and function. Beta blockers have been reported to have different effects on these organ functions depending on their degree of ISA and cardioselectivity. Noncardioselective β blockers without ISA, such as propranolol, may decrease both glomerular filtration rate (GFR) and renal blood flow (RBF), whereas β blockers with ISA, such as pindolol (a precursor of bopindolol), have no adverse effect on renal function. Three reports on renal function were presented in this symposium.

Miyajima et al presented the results of an investigation of the long-term effect of bopindolol on renal function in the supine and upright positions and its relation to humoral factors in 11 patients with essential hypertension. Following 24 weeks of bopindolol treatment, GFR and RBF were significantly increased in both positions and accompanied by a reduction of renal vascular resistance. The mechanism of renal improvement is explained by the ISA of bopindolol and its suppression of renin activity.

Goren et al reported on the chronic effect of bopindolol on creatinine clearance following normalization of blood pressure (diastolic blood pressure <90 mm Hg) in 15 patients with essential hypertension. Creatinine clearance was well maintained within the normal range, increasing from 111 ± 8 to 116 ± 6 ml/min, with good control of blood pressure, which fell from 159 ± 7/102 ± 3 to 129 ± 7/82 ± 2 mm Hg without significant side effects.

Ideura et al attempted to clarify the favorable renal influence of bopindolol in hypertensive patients with renoparenchymal disease. The patients' initial serum creatinine varied from 0.7 to 6.9 mg/dl with a mean value of 3.0 mg/dl. In 58% of the patients, blood pressure fell from a mean of 180 ± 2/100 ± 2 to 161 ± 8/90 ± 5 mm Hg ($p < 0.05$) following 12 weeks of bopindolol treatment.

Bopindolol had no adverse effect on renal function. Serum creatinine changed from 3.0 ± 0.6 to 3.3 ± 0.8 mg/dl (not significant); in 3 cases with renal failure it was demonstrated that this was not attributable to bopindolol. Pharmacokinetic studies of oral bopindolol in patients with chronic renal failure or in hemodialysis were also performed. Although $t_{1/2}$ was slightly prolonged, it was concluded that the normal dosage of bopindolol can be safely administered to these patients.

These observations indicate that the normal dosage of bopindolol may have a favorable effect on the kidney in patients with various degrees of renal impairment as well as in patients with primary kidney disease.

Clinical and epidemiologic evidence has accumulated to support the proposition that left ventricular hypertrophy (LVH) is an independent risk factor for cardiovascular morbidity and mortality in hypertensive patients, and regression of LVH by pharmacological intervention has been extensively investigated for all classes of antihypertensive agents. However, the results of studies of β blockers are somewhat controversial.

Saragoca et al presented the results of a study of the cardiac effect of bopindolol in hypertensive patients with LVH. Long-term bopindolol treatment resulted in reduction of LV mass from 201 ± 21 to 130 ± 13 g, with an 80% response rate at 9 months. Pump function (ejection fraction) was maintained without deterioration following reversal of LVH. This study indicates that bopindolol has a favorable effect on cardiac structure and function in patients with hypertensive complications.

Antianginal effect: Beta blockers are one of the 3 main classes of antianginal agents. In spite of their differing pharmacological characteristics, all the various β blockers appear to have similar effects in the relief of effort angina.

Meyer et al compared the antianginal efficacy of bopindolol versus that of the calcium antagonist diltiazem in stable angina pectoris. Eight weeks of treatment with each drug was evaluated clinically using a patient diary of episodes of pain and a treadmill exercise tolerance test. Bopindolol caused a significant reduction in the frequency of anginal attacks (reduced by 22/month in the bopindolol group vs 1.65 in the diltiazem group; $p < 0.05$) and improvement in exercise tolerance (exercise time increased by 1.5 min vs 0.66 min; $p < 0.05$), indicating that bopindolol was more effective than diltiazem.

The antianginal efficacy of bopindolol was further evaluated in comparison with another β blocker, atenolol, in 2 double-blind studies. Hertzeanu et al assessed the therapeutic efficacy of bopindolol and atenolol on the frequency of anginal attacks and exercise tolerance in a double-blind randomized trial in 29 patients with stable angina pectoris. Clinical and anginal characteristics did not differ between the 2 groups. Three months of treatment with either β blocker showed a comparable effect on exercise tolerance with no rebound phenomenon; however, bopindolol was more effective in the reduction of anginal attacks than atenolol (2.45 vs 3.29 attacks). It was observed that a stepwise increase of dosage (0.5 to 2 mg of bopindolol, 50 to 200 mg of atenolol) was not associated with an improvement of efficacy of either drug.

Michaelides et al obtained the same results as Hertzeanu et al. They also evaluated the effect of bopindolol on exercise capacity in a double-blind study versus atenolol in 20 patients with stable angina pectoris. They administered a fixed dose of 1 mg bopindolol or 100 mg atenolol for 20 weeks. Exercise tolerance improved similarly with both drugs in terms of exercise duration, ST-segment change and ischemic threshold. In summary, bopindolol may have anti-ischemic efficacy similar to that of commonly used antianginal agents, in addition to being effective and safe. Further studies focusing on silent ischemia are required.

CONCLUSION

The clinical characteristics, efficacy and usefulness of bopindolol in hypertension and angina pectoris were indicated by most of the studies presented at the symposium. Bopindolol lowered blood pressure effectively and was well tolerated with fewer or comparable side effects compared with other antihypertensive agents. Its effects on lipid metabolism and platelet aggregation were favorable. Bopindolol does not affect renal function. It causes regression of hypertensive cardiac hypertrophy. Bopindolol is also effective for angina pectoris.

Antihypertensive drugs are expected to reduce cardiovascular morbidity and mortality and to reverse abnormalities of core organs, including cardiovascular hypertrophy, in addition to the primary aim of lowering blood pressure.

Bopindolol thus appears to satisfy the requirements of an antihypertensive agent. The results of clinical studies of whether bopindolol is able to prevent myocardial infarction will be available in the near future.

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MAY 6, 1991

A Symposium: Proceedings of the Second International Heart Failure Workshop

GUEST EDITOR:
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Professor of Medicine
University of California San Francisco
Chief of Cardiology
Moffitt/Long Hospitals
San Francisco, California

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A SYMPOSIUM: PROCEEDINGS OF THE SECOND INTERNATIONAL HEART FAILURE WORKSHOP

1C
Introduction
William W. Parmley

3C
Neuroendocrine Activation in Congestive Heart Failure
J. Colin Forfar

6C
Local Cardiac Responses — Alternative Methods of Control
Bernhard Maisch

11C
Panel Discussion

13C
Adrenergic Receptor Responsiveness and Congestive Heart Failure
Gary L. Stiles

18C
Cardiac Beta-Adrenoceptor Regulation and the Effects of Partial Agonism
David B. Barnett and Xianyou Lu

20C
Interrupting the Adaptive Changes in Congestive Heart Failure
Wolfram Kupper

23C
Panel Discussion

26C
Genesis of Arrhythmias in the Failing Heart and Therapeutic Implications
Celia Oakley

29C
Adaptive Changes in the Periphery and Their Therapeutic Consequences
Helmut Drexler, Thomas Münzel, Urs Riede, and Hanjörg Just

36C
Assessment of Exercise Tolerance in Chronic Congestive Heart Failure
Alain Cohen Solal and René Gourgon

41C
Assessment of Quality of Life
David B. Barnett

45C
Workshop Discussion

48C
Acute and Chronic Hemodynamic Effects of Xamoterol in Mild to Moderate Congestive Heart Failure
Surinder J.S. Virk, Fengxia Qiang, Nicholas H. Anfilogoff,
Robert G. Murray, William A. Littler, and Michael K. Davies

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Introduction

William W. Parmley, MD

One of the most interesting chapters in our understanding of the pathophysiology of congestive heart failure (CHF) has been the role of the neuroendocrine systems that are activated in heart failure. One of the most influential principles to emerge over the past decade is the fact that compensatory mechanisms such as these are initially helpful to the cardiovascular system, but they then overshoot and become detrimental. Although this is an oversimplistic characterization of what happens during the development of CHF, it is one of the most important concepts underlying therapeutic interventions which benefit the myocardium and the circulatory system. This symposium is designed to evaluate further the role of neuroendocrine systems, particularly the catecholamines, in CHF and the potential for therapeutic intervention.

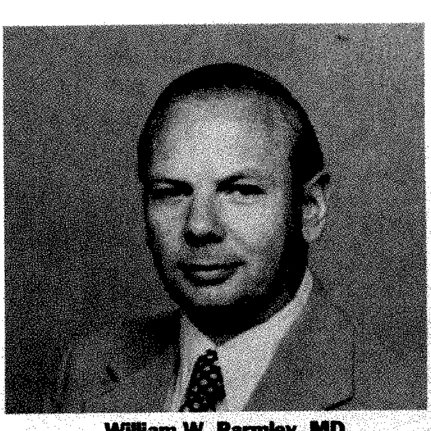
Forfar reviews the overall changes that occur in the sympathetic nervous system and the renin-angiotensin system in CHF. Stiles details the complex interactions that underlie the action and regulation of the receptor-adenylate-cyclase systems. Knowledge of the distinct, integral membrane protein components and their interaction has been of great importance in understanding so-called up- and down-regulation. It is clear from Stiles's elegant discussion that not only is our information base continually changing in this area, but also there is an opportunity to consider many therapeutic agents that could intervene at various points in the receptor adenylate-cyclase system. Maisch discusses some of the interesting non–β_1-receptor cardiac control mechanisms.

Kupper describes how treatment with drugs such as xamoterol, which reduce the activity of the sympathetic nervous system, can help to break the vicious circle of ventricular dysfunction, fluid retention and reflex vasoconstriction.

Barnett and Lu discuss the interesting concept of partial agonism. The intriguing possibility that a drug could be used to block the harmful effects of excess catecholamine secretion, but at the same time support the circulation with partial agonism, is discussed. Data with xamoterol, a representative compound with these properties, are reviewed. The fact that xamoterol does not induce down-regulation, suggesting that with this kind of approach, responsiveness of the β receptors can be maintained, while at the same time blocking the effects of excess catecholamines, is of some interest.

Oakley describes one of the most difficult aspects of the management of patients with severe CHF (namely, the presence of life-threatening ventricular arrhythmias). Although the mode of death is sudden in approximately 40% of patients with heart failure, there are no firm data indicating that this adverse outcome can be altered. Some drugs that improve left ventricular function, such as the angiotension-converting enzyme inhibitors, have been shown to reduce ventricular premature complexes, although no therapy has been shown to reduce the incidence of sudden death. The important dilemma of whether to consider antiarrhythmic therapy is faced by the clinician each day. Unfortunately, we have no firm data at the moment to assure us that this therapy can benefit patients.

Although much attention in this symposium is naturally focused on the heart and the effects of the catecholamine system, there is a wide variety of peripheral changes occurring in CHF that are summarized by Drexler and co-workers. It is, in fact, many of these peripheral changes that set the stage for therapeutic interventions such as afterload reduction. A better understanding of the events occurring in peripheral vessels and in skeletal muscle leads to a number of therapeutic interventions which may have little or no direct effect on the heart.



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One of the great challenges to the clinician has been the assessment of the clinical status of patients and their response to therapeutic interventions. Exercise testing is one means of assessing the response of the patient to therapeutic intervention. Cohen Solal and Gourgon review exercise testing as a quantitative measure. They conclude that there are problems with using this index of improvement, although it remains one of the more important objective measures.

Barnett explores the interesting question of how to measure quality of life. It has been known for many years that there may be only a tenuous relation between quantitative measures of ventricular performance and either exercise tolerance or quality of life. To most patients, improvement in their quality of life is a far greater goal than any improvement in cardiac output or other hemodynamic parameters. Although it is difficult to assess quality of life in a meaningful way, this area of evaluation will become increasingly important in determining the outcome of different therapeutic interventions.

Last, Virk et al review the acute and chronic hemodynamic effects of xamoterol, a β_1 partial agonist, in mild to moderate heart failure. These studies suggest that a partial agonist can improve cardiac function both at rest and during exercise with minimal adverse effects and thus be a reasonable therapeutic alternative in patients with mild to moderate heart failure. The use of this agent is a natural extension of the concepts and principles related to neuroendocrine activation, as discussed in this symposium. Overall, it is clear that as our knowledge expands on the importance of the activation of several different hormonal systems, our therapeutic alternatives will increase and allow us to modify beneficially hemodynamics, exercise tolerance, and quality and duration of life.

Neuroendocrine Activation in Congestive Heart Failure

J. Colin Forfar, MD, PhD

Several changes in neuroendocrine activity follow failure of cardiac function to satisfy peripheral requirements and contribute to the clinical syndromes of heart failure. Afferent pathways are poorly understood and triggers are both central and peripheral, involving attenuation of atrial and arterial baroreceptor activity. Efferent sympathetic activity is generally increased with resulting vasoconstriction, but responses are organ-specific and differ among heart, kidney, lung and skeletal muscle. Changes in cardiac sympathetic activity are inadequately understood. Enhanced cardiac norepinephrine spillover contrasts with reduced tissue concentration and impaired activity of synthetic enzymes and neuronal catecholamine uptake. Beta-receptor down-regulation further complicates overall adrenergic responsiveness and the balance between enhancement of contractile function and reduction in arrhythmia threshold. Activation of the renin-angiotensin system is potentiated by the sympathetic nervous system and may contribute to vasoconstrictor hyporesponsiveness. Angiotensin II may in turn facilitate the central and peripheral effects of sympathetic activation and the release of vasopressin from the pituitary. Our understanding of the role of vasodilator peptides in heart failure remains rudimentary. It is likely that vasoconstrictor neuroendocrine response adversely influences optimal cardiac funtion in heart failure and may promote arrhythmogenesis. The neuroendocrine response in individual organs, however, requires intensive study.

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Reduction in myocardial performance has the potential to trigger a number of neuroendocrine mechanisms, presumably intended to preserve circulatory homeostasis acutely, but which have the potential when applied chronically to promote a clinical syndrome readily recognizable as heart failure. In the short term, activation of the sympathetic nervous system and release of vasoconstrictor peptides may maintain systemic blood pressure and augment cardiac output. In the longer term, however, endogenous vasoconstrictor neurohormones increase the loading of the failing heart, and may contribute to progression of the underlying disease process. The reflexes triggered are similar to those activated in response to intravascular volume depletion, but in heart failure the balance between a potentially beneficial role with maintenance of blood pressure, cardiac contractile function and renal perfusion is weighed less certainly against inappropriate vasoconstriction. Organ responses are further complicated by alterations in sensitivity to a variety of stimuli and changes in transmembrane signaling. These changes may be organ-specific and differ between, e.g., the heart and the kidney. Despite these complexities, some attempt to assess the individual components of this complex physiologic response is appropriate.

CIRCULATORY REFLEXES

Much still remains to be learned about the changes in the function of neurocirculatory reflexes in heart failure. The proportion of afferent nerve input from the heart, great vessels and periphery is unknown. However, it is established that atrial and arterial baroreceptor function is impaired, resulting in reduced tonic inhibition of sympathetic activity and central release of vasopressin.[1-3]

The mechanism causing impaired baroreceptor control in heart failure is not yet established. Some work on animals has suggested that baroreceptor control of heart rate remains depressed for several months after reversal of heart failure,[4] suggesting structural changes in the baroreceptors themselves. On the other hand, recent studies in patients who have undergone heart transplantation have suggested that baroreceptor reflex sensitivity was similar to normal controls and greater than in patients with severe heart failure.[5]

In 3 patients in this study, the arterial baroreflex slope could be measured both before and after cardiac transplantation. In each patient there was a striking increase in the baroreflex slope after transplantation. Recovery of baroreceptor sensitivity occurred as early as 2 weeks after transplantation despite concomitant medication, making it less likely that the depressed responses resulted from structural alterations in the baroreceptors themselves.

SYMPATHETIC NERVOUS SYSTEM

At first sight, generalized activation of the sympathetic nervous system appears to be a uniform accompaniment of heart failure. We have known for many years that urinary norepinephrine excretion increases progressively with increasing severity of heart failure.[6]

This increase in excretion is paralleled by elevation of plasma norepinephrine concentration that correlates directly with the degree of left ventricular dysfunction, as reflected by pulmonary capillary wedge pressures and indexes of systolic contraction.[7,8] During exercise in patients with heart failure, plasma catecholamine concentrations increase to a greater extent than in normal subjects,[9] although such a response could reflect reduced catecholamine clearance as well as an increase in plasma catecholamine spillover. However, this view of generalized neurosympathetic activation is simplistic and fails to take into account a number of pathophysiologic phenomena operative in heart failure.

First, there is evidence for regional specificity in blood flow in heart failure. Skeletal muscle blood flow is reduced both at rest and during exercise, whereas coronary blood flow may not change as a result of the heart failure state. Renal perfusion can change dramatically during exercise. Recent studies in Oxford[10] using isotope renography have shown profound reduction in isotope uptake during exercise in patients with New York Heart Association class III heart failure, almost certainly reflecting renal artery vasoconstriction.

Second, it has been known for several years that end-organ responsiveness to a given catecholamine stimulus may be modified as a result of heart failure. Ventricles from patients with heart failure show reductions in β-adrenoceptor density and in agonist-stimulated adenylate cyclase production and contractile responses.[11] It is uncertain whether this mechanism for desensitization is a consequence of augmented efferent cardiac sympathetic tone or a primary response of severely diseased heart muscle. In any event, the intrinsic contractile state of cardiac muscle does not seem to depend on local catecholamine stores.[12] One of the pitfalls of apparent alteration in sympathetic responsiveness was illustrated recently by comparison of dose-response curves for heart rate using an intravenous infusion of isoproterenol and epinephrine in patients who had undergone heart transplantation.[13] Heart rate responses for the denervated (transplanted) atria and innervated (native) atria were compared within the same patient. The dose-response curve to epinephrine was clearly shifted to the left (an increase in organ sensitivity) when comparing the denervated and innervated atria. In contrast, no change in dose-response curves between the denervated and innervated atria were shown for isoproterenol. The investigators explained this difference in terms of a presynaptic effect; the presence of sympathetic nerve terminals in the innervated atria could remove epinephrine through the uptake 1 mechanism, and thus reduce the concentration of epinephrine in the synaptic cleft, whereas no such removal mechanism is operative for isoproterenol.

Our understanding of cardiac sympathetic activity in heart failure is fragmentary. It appears that tissue norepinephrine concentrations are reduced in experimental heart failure models and in both atrial and ventricular myocardium in a variety of clinical heart failure syndromes.[14] However, studies in humans using radiotracer kinetic techniques have suggested that cardiac catecholamine spillover from the heart is significantly increased in patients with heart failure at rest,[15] and that there is a further increase in spillover during exercise.[16] Organ-specific catecholamine spillover in heart failure varies, being increased from heart and kidney, but not significantly increased from the lung, the latter organ being a major contributor to total catecholamine production. These data are difficult to reconcile with evidence that neuronal reuptake of norepinephrine may be impaired in heart failure in humans,[17] and that the activity of tyrosine hydroxylase and dopamine hydroxylase may be impaired in some experimental heart failure models.[18,19]

RENIN-ANGIOTENSIN SYSTEM

There is good evidence that the degree of activation of the renin-angiotensin system depends largely on the clinical state of the patient. Thus, patients with recent onset of pulmonary edema or acute or chronic congestive heart failure tend to have higher plasma concentrations of angiotensin II and a higher plasma renin activity than patients with chronic stable congestive heart failure.[20] Similarly, clinical improvement after acute decompensation is associated with a reduction in activity of the renin-angiotensin system despite persistence of severe cardiac dysfunction. Acute activation of this pathway may follow a decrease in systemic blood pressure associated with reduced cardiac output. It is likely that the variable status of the renin-angiotensin system in congestive heart failure is related in part, to heterogeneity of clinical status of the patients studied.

Drug therapy clearly influences renin-angiotensin activation. In mild to moderate heart failure, plasma renin activity and plasma aldosterone may be normal before diuretic treatment, but plasma norepinephrine concentrations appear to be elevated at an early stage.[21] After treatment with diuretics, changes in the activity of the renin-angiotensin and sympathetic nervous systems have been observed with an increase in renin activity and aldosterone concentration, and a decrease in plasma norepinephrine. These changes were observed in the presence of a substantial increase in exercise duration after diuretic treatment. If the increase in renin activity after administration of diuretics acts to limit diuretic-induced increases in exercise capacity, it would be logical to consider angiotensin-converting enzyme inhibition as concomitant therapy with diuretics in the long-term management of chronic heart failure.

There is the potential for important interactions between the adrenergic and renin-angiotensin-aldosterone systems. Theoretically, this can occur at several levels. Efferent sympathetic activity directly releases renin from the kidneys, a β_1 receptor-mediated phenomenon recognized for several years. Additionally, however, presynaptic interactions may occur. At low concentration, angiotensin II facilitates norepinephrine release from the sympathetic nervous terminal by way of presynaptic angiotensin II receptors. At a higher concentration, a tyramine-like action of angiotensin II may directly promote norepinephrine release. The role of these mechanisms in determining regional blood flow in clinical heart failure is uncertain. Postsynaptic α adrenoceptors may be sensitized as a result of activation of postsynaptic angiotensin II receptors.[22] There is also the possibility of direct attenuation of baroreceptor sensitivity by angiotensin II.[23]

OTHER HORMONES

It is unclear how much the elevation in the concentration of vasopressin contributes to elevation in systemic vascular resistance in congestive heart failure.[3] Similarly, the role of atrial natriuretic peptide as a counter-regulatory system for vasodilation and sodium balance is uncertain,[24] as is the role of other vasodilators, including prostaglandins and bradykinin.

It is likely that complex neuroendocrine interactions with a multifactorial basis underlie the responsiveness of individual organs in heart failure. It is probable that important differences exist between heart, lungs, kidneys and skeletal muscle. The concept of an overall "average" response may not be appropriate.

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Local Cardiac Responses — Alternative Methods of Control

Bernhard Maisch, MD

Much attention has been paid to the influence of the β-adrenoceptor system on cardiac function in heart failure. Full agonists and partial agonists acting on cardiac β_1 receptors have been widely investigated, as has the density of these receptors in the failing heart. However, other cardiac control mechanisms may play important roles in the normal heart as well as in heart failure. The Frank-Starling mechanism of enhanced cardiac contraction produced by mechanical stretching of the ventricular myofibrils is well known. When treating patients with heart failure with diuretics, vasodilators and other drugs that influence preload, it is important to consider their overall effects in relation to the Starling curves. Atrial stretching also produces compensatory responses which are currently being intensively studied. Reflex release of atrial natriuretic factor after stimulation of atrial receptors has important physiologic effects in heart failure. The atria, but not the ventricles, are innervated by the vagus; the influence of the parasympathetic nervous system on the heart and circulation is often overlooked. The initial increase in heart rate during exercise is primarily due to withdrawal of vagal influence. Besides acetylcholine, the parasympathetic transmitter, many other local hormones may affect cardiac function; these include prostaglandins, 5-hydroxytryptamine and histamine. Although the activity of the sympathetic nervous system is mediated primarily through β_1 adrenoceptors, both β_2 and α receptors are also found in the heart. Myocardial α_1 receptors, which mediate a positive inotropic effect, have been identified, and prejunctional α_2 receptors may mediate inhibition of norepinephrine release from sympathetic nerves. Cardiac β_2 receptors are believed not to be innervated, but represent hormonal adrenoceptors that are responsive to circulating adrenaline and exogenous stimulation. The importance of many of these non–β_1-receptor cardiac control mechanisms is little known, but further pharmacologic work is continuing which may elucidate their role in both the normal and failing heart.

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Cardiac output is primarily determined by 4 factors: heart rate, preload, afterload and contractility. In turn, cardiac output, along with heart rate and myocardial oxygen consumption, is a major determinant of normal cardiac function. In patients with heart failure, however, compensatory mechanisms that would normally correct an acute decrease in cardiac output can produce a deterioration in cardiac function, leading to a further decrease in cardiac output.

In acute heart failure, a reduction in cardiac output can be compensated for by means of the Frank-Straub-Starling mechanism, humoral factors and the activity of the autonomic nervous system. In chronic heart failure, however, the importance of these adaptive changes diminishes, and humoral and autonomic regulation eventually produces structural adaptations such as hypertrophy and fibrosis. This accounts for the clinical findings of hypertrophy and dilatation seen in patients with advanced disease.

This report will examine the clinical significance of the various mechanical, autonomic and endocrine responses seen during acute and chronic heart failure. It should be borne in mind, however, that while the interactions between these responses in humans are complex, attempts to use simpler models present difficulties. Care must be taken, e.g., in extrapolating data derived from experiments with intact animals to the clinical situation. Isolated heart muscle and myocytes are free from autonomic nervous control and only certain factors can be studied in these systems.

MODULATION OF VAGAL TONE

An increase in catecholamine concentrations is associated with a decreased vagal tone and a consequent increase in heart rate. A classic instance of this form of cardiac control is exercise.

MECHANICAL RESPONSES

The Frank-Starling mechanism: The relation between ventricular peak systolic pressure and end-diastolic volume is shown in Figure 1. In the normal heart,[1-3] an increased diastolic volume produces an increase in force of contraction and stoke volume. In heart failure, however, the ventricle dilates and must develop a higher tension to produce a given pressure; this results in a reduced dP/dtmax (the maximal rate of pressure rise in the ventricle) and stroke volume.

The volume-stress relation: The relation between wall stress and left ventricular volume in the normal heart and during heart failure is shown in Figure 2. In heart failure, end-diastolic volume and pressure are higher than normal and, as failure progresses, the ejection fraction decreases and the residual volume increases. The efficiency of contraction thus decreases, leading to a decrease in cardiac output.[4] Additionally, the afterload on the ventricle may change during ejection itself. When the preload reserve in heart failure is reached, afterload mismatch is observed.[5]

Effects of stretching: Studies with isolated isometrically contracting papillary muscles show that abruptly stretching the muscle leads to a time-dependent increase in contractile force accompanied by a slow relaxation with another time constant,[6,7] which does not depend on exogenous hormonal stimulation (Fig. 3). It has been partly explained by viscoelastic changes and relative prolongation of the action potential,[6,7] but may also reflect a release of endogenous tissue hormones. Histologic studies show dense granules in the atrium[8]; these were originally believed to contain catecholamines, but are now known to contain atrial natriuretic peptide (ANP).[8-11] The effects of ANP tend to interrupt the "vicious circle" of heart failure, in which activation of the sympathetic nervous system and the renin-angiotensin system produces reflex venoconstriction and water retention which increase preload and afterload, leading to a further deterioration in ventricular function. ANP has a mild diuretic effect and reverses the venoconstriction produced by the sympathetic nervous system and by vasopressin. Infusion of ANP in healthy subjects has little effect on heart rate, while mean arterial pressure, cardiac index and pulmonary wedge pressure may be slightly but significantly reduced[12] (Fig. 4). In patients with congestive heart failure, there is a more marked change in pulmonary wedge pressure and a slight decrease in mean arterial pressure (Fig. 5).[12,13] This leads to an increased cardiac output that is not seen in healthy subjects.

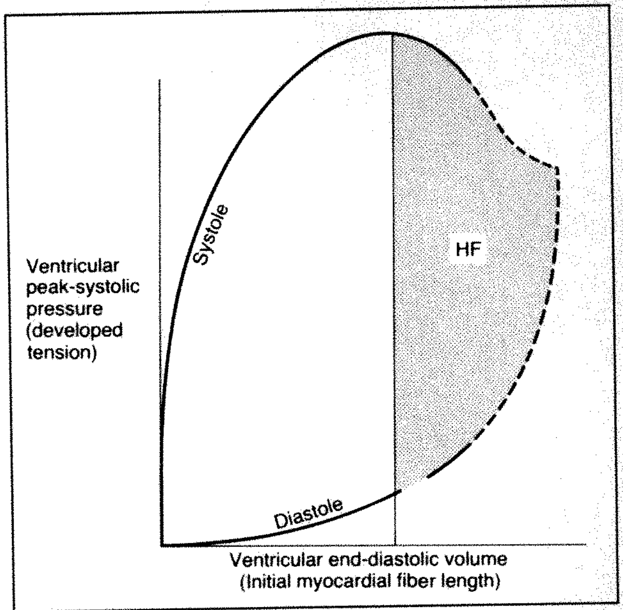

FIGURE 1. Frank-Straub-Starling pressure-volume relation. *Solid line* represents data from men and experimental animal in situ; *broken line* is only partly from in situ experiments but represents data from isolated heart muscle preparations. HF= heart failure.

LOCAL HORMONES

Alpha-adrenergic agonists: Catecholamines acting at α adrenoceptors activate phospholipase C, which converts phosphatidylinositol 4,5-biphosphate to inositol, 1,4,5-triphosphate (ISP_3) and diacylglycerol. ISP_3 then causes the release of intracellular calcium, which leads to increased contractility. This effect is mediated by postsynaptically located adrenoceptors of the α_1 type.[14] The positive inotropic response develops relatively slowly

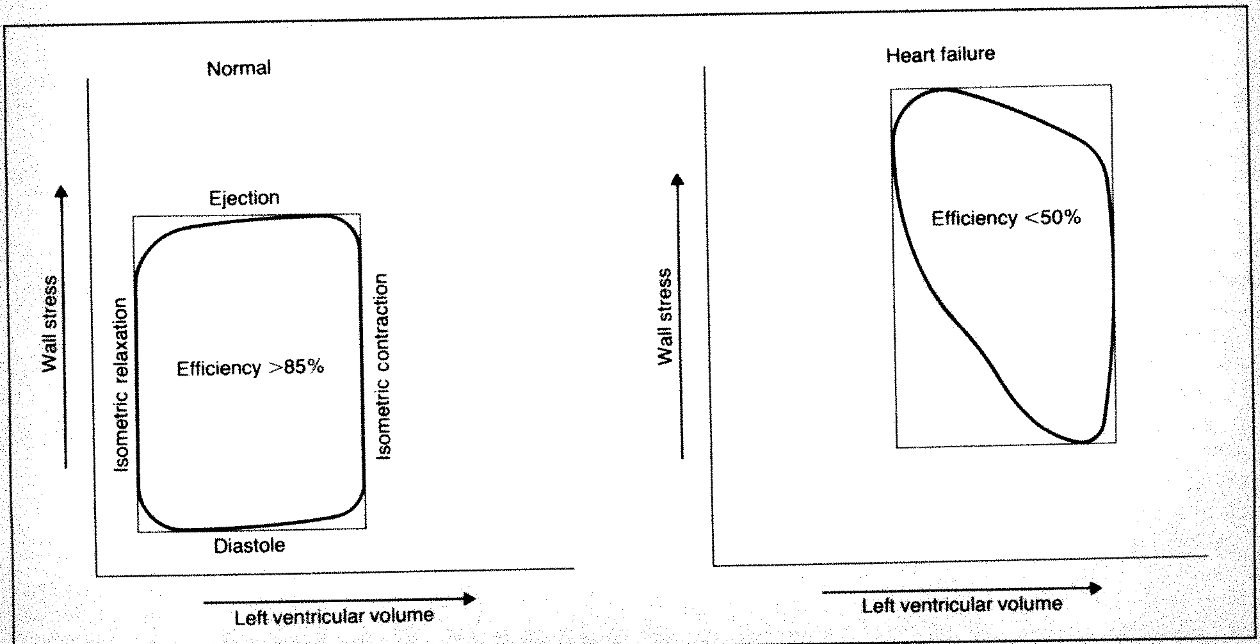

FIGURE 2. Relation between wall stress and left ventricular volume in the normal heart and during heart failure. (Reprinted with permission from *Eur Heart J.*[4])

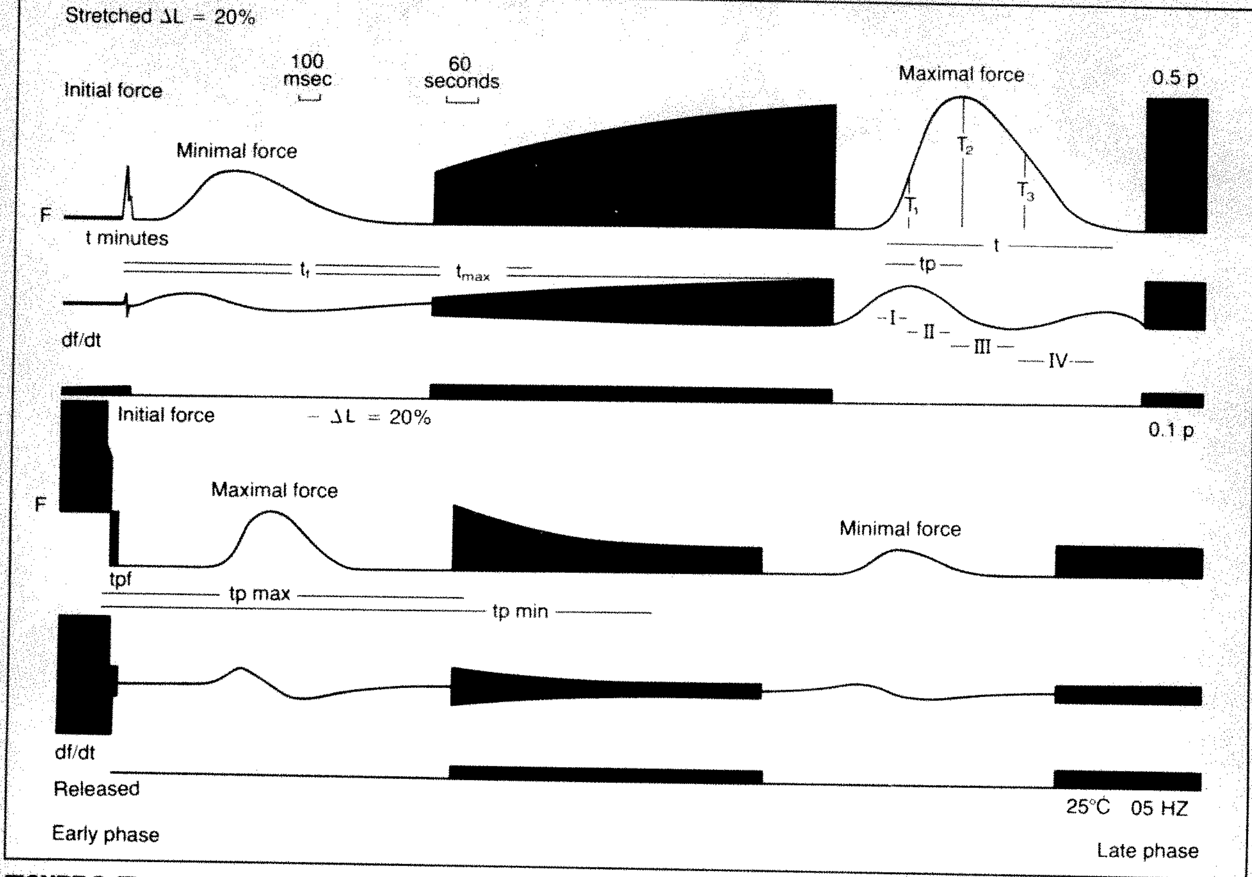

FIGURE 3. Time-dependent increase in force after stretching of isolated feline papillary muscle during continuous electrical stimulation. After stretching of the papillary muscle by 20% of its initial length (L = 20%), the initially developed force is reduced after t min, which corresponds to 7 to 10 contractions and a minimal force is observed. Although relaxation continues until t_f has passed, isometric contraction continuously increases for 8 minutes (tmax) until maximal force is reached. This applies not only to force (F) but also to its first derivative (df/dt). After a release to the initial length (lower part of the original registration) a slight increase of diastolic tension is observed during tpf. Initial force increases rapidly until maximal force is reached within 30 to 60 seconds (tp max). A gradual decrease of force follows until a constant isometric force is reached within 7 to 10 minutes (tp min). For stretch and release experiments, alterations of the plateau phase duration of the action potential may be a partial explanation. Involvement of local hormones offers another, speculative alternative. (Adapted from *Basic Res Cardiol.*[6])

within minutes and is accompanied by an increase rather than a decrease in the duration of contraction when compared with the β-adrenergic response.[14,15] The antihypertensive drug clonidine has a vasoconstrictor effect mediated by postsynaptic α_2 receptors in the peripheral vasculature; its antihypertensive effect is due to an action on control α receptors in the medulla oblongata, which leads to a reduced cardiovascular drive.

Histamine: In humans, only H_2 receptors are identifiable; their stimulation leads to intracellular uptake of calcium and enhanced contractility.[16] Einstein et al[17] studied the effects of histamine in the innervated or denervated canine heart. When blood pressure was kept constant, histamine caused a decrease in heart rate in the innervated heart only. In the denervated heart and in isolated cultured heart cell preparations, histamine increases the beating frequency by increasing verapamil-sensitive sodium influx. Both the inotropic and chronotropic effects are supposedly mediated by H_2 receptors coupled to adenylate cyclase.[18] The major effect was on contractility; contractile force increased to a greater extent in the denervated than in the innervated heart. A long-acting analog of histamine, impromadine, has a similar effect on heart rate and contractile force.[19] H_2 antagonists, such as cimetidine, exert the opposite effect by inhibition of the verapamil sensitive Na^+ influx which was initially enhanced by histamine.

5-Hydroxytryptamine: 5-Hydroxytryptamine (5-HT) can produce vasoconstriction in coronary arteries. This effect may interact with the effect of thromboxane A_2 also derived from aggregated platelets, and may be facilitated by catecholamines and angiotensin II. The 5-HT_2 antagonist ketanserin produces an increased stroke volume, but also decreases heart rate, so cardiac output decreases slightly.

PURINOCEPTORS

Purinoceptors are classified into P_1 and P_2 subclasses on the basis of available selective antagonists and agonists.[20] The P_1 purinoceptor is characterized by the antagonists theophylline, caffeine and 8-phenyltheophylline, which antagonize the decrease in force caused by stimulation of the P_1 purinoceptor, thus exerting a positive inotropic and also a positive chronotropic effect. P_2

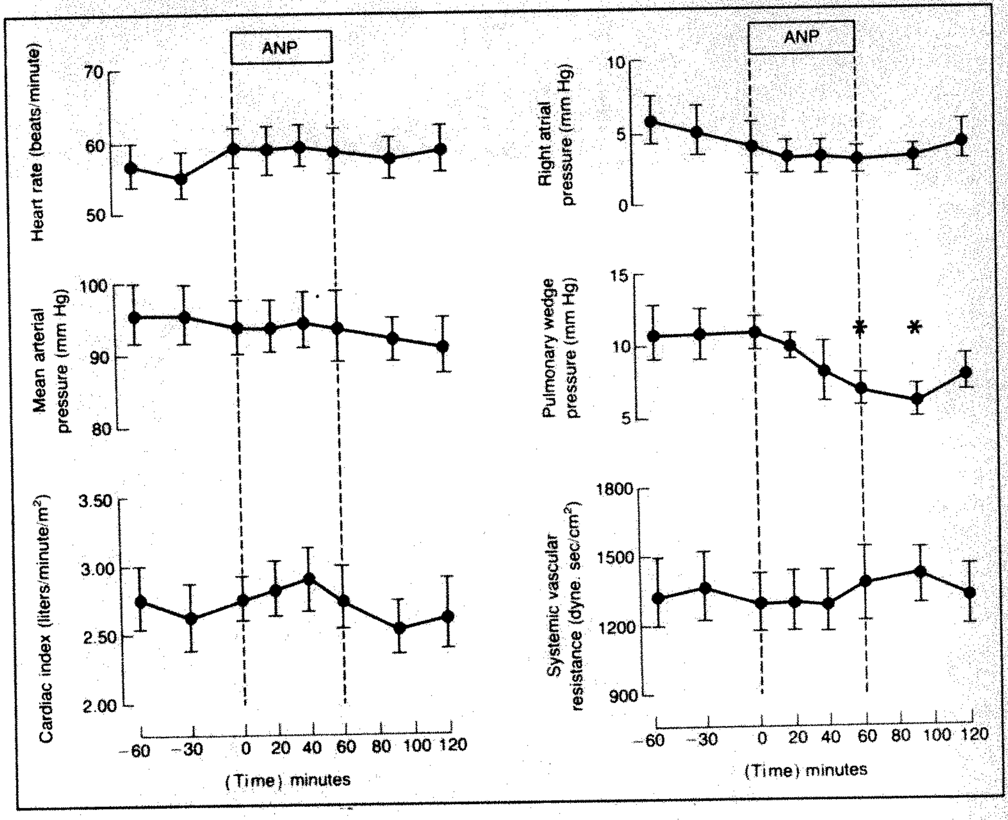

FIGURE 4. Effects of atrial natriuretic peptide (ANP) infusion in healthy subjects (values are mean ± standard error of the mean). (Reprinted with permission from *J Clin Invest.*[12])

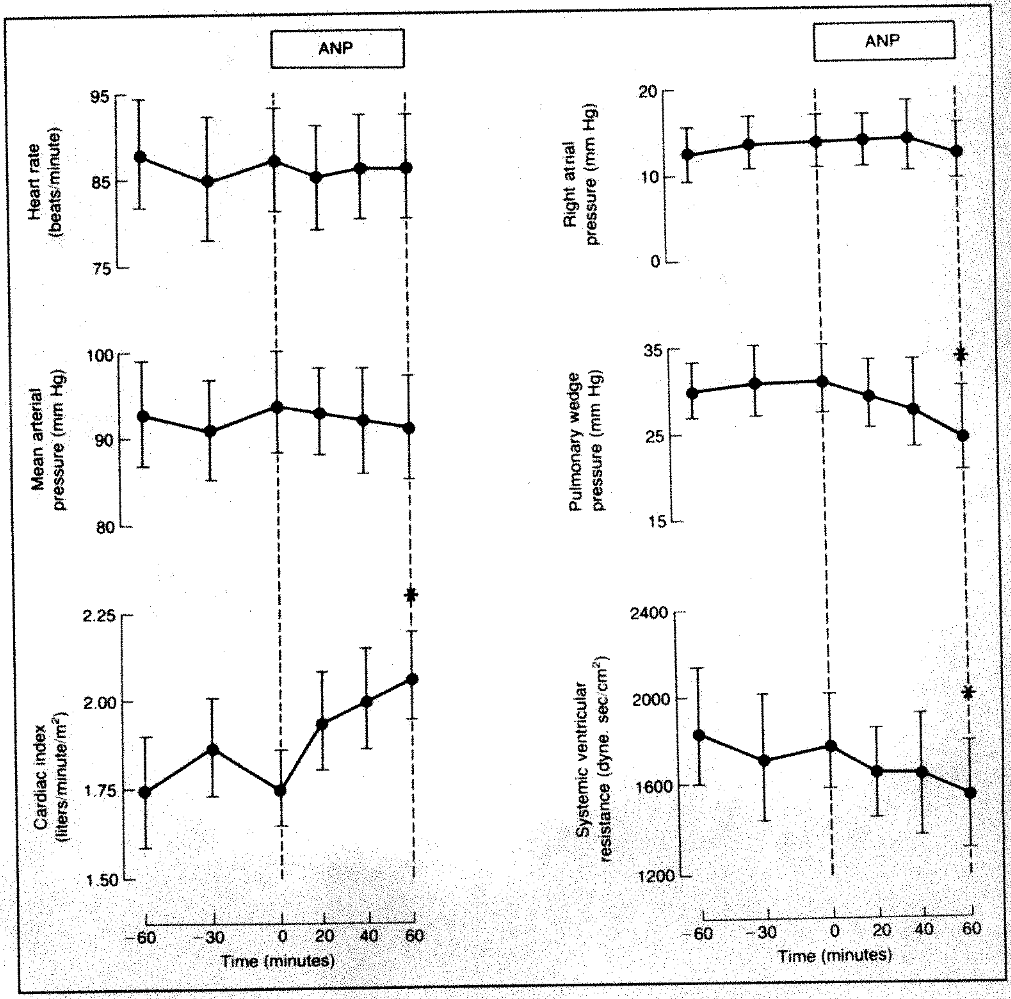

FIGURE 5. Effects of atrial natriuretic peptide (ANP) infusion in patients with congestive heart failure (values are mean ± standard error of the mean). (Reprinted with permission from *J Clin Invest.*[12])

purinoceptors are activated by the direct agonist adenosine, which decreases contractile force and sinoatrial pacemaker activity, and may induce vasoconstriction of renal arteries and coronary vasodilation. Dipyridamole may potentiate several cardiac effects of adenosine by an extracellular accumulation of adenosine and inhibition of adenosine diffusion. It also inhibits the activity of the intracellular enzyme adenosine deaminase in higher concentrations. It is used clinically to assess coronary blood flow and coronary reserve.

CARDIAC PROSTAGLANDINS

Cardiac prostaglandins (PGs) produce a variety of complex effects on cardiac tissue. They depend on the type of PG, the dose used and the animal species in which the experiments are performed.[21] In vivo experiments demonstrated that PGE_1 and PGE_2 may increase contractile force in humans and may induce tachycardia, whereas PGF_2 had no effect on contractile force when injected into the coronary artery of the mammalian canine heart. In humans, an increase in blood pressure and a decrease in heart rate were observed. These diverse effects were considered to be of reflex origin. After in vivo and in vitro studies, there still remains uncertainty regarding the role of endogenous prostaglandins in regulating or modulating cardiac function.[21]

CONCLUSIONS

The contribution of β adrenoceptors and classic mechanical responses, such as the Frank-Straub-Starling relation, to the control of the heart have been extensively studied. Other factors such as ANP and local hormones are less well understood; the interactions between these are often complex and need further investigation.

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Panel Discussion

Dr. Groebecker (Federal Republic of Germany): With regard to the distribution of β_1 and β_2 receptors, which of the β receptor populations is primarily downregulated by the enhanced release of norepinephrine and epinephrine?

Dr. Maisch (Marburg, Federal Republic of Germany): There is good evidence that β_1 receptors are downregulated more than the β_2 receptor population, but that is usually in the end stages of heart failure. Most work has been conducted on transplanted hearts, using the end-stage heart failure model.

Dr. Camerini (Italy): What is the role of vasodilating agents in congestive heart failure? It is said that administration of anti-inflammatory nonsteroidal drugs (NSAIDs) to patients with heart failure may result in deterioration of these patients due to their action on prostacyclin.

Dr. Forfar (Oxford, United Kingdom): I think most of that information is anecdotal but there is a good basis, particularly in the kidney, for a deleterious effect, and particularly a deleterious interaction between the vasoconstrictor hormones and the local renal regulatory release of the prostaglandin E series, and also perhaps prostacyclin. As far as the heart is concerned, our knowledge of these interactions is so rudimentary that it is very difficult to get a composite picture of the interplay among these factors. We have heard about the presynaptic receptor agonists and antagonists that may potentially interact, but this is only the tip of the iceberg; up to 15 or 20 different peptides and autocoids may be playing a regulatory role. Our understanding is too rudimentary to analyze the individual effects.

Dr. Maisch: Research on the kidney provides evidence that prostacyclin may deleteriously affect myocardial function. In my patients I have not seen a deleterious effect of nonsteroidal drugs or of steroids. On the contrary, a proportion of patients have benefited following administration of NSAIDs or steroids. From a clinical point of view the importance of the genetic component involved in this form of heart disease has to be considered. If inflammation occurred in patients with secondary heart muscle disease, I would not hesitate to use anti-inflammatory drugs, despite the possible negative effect that has been alluded to, but if there is little inflammation I would consider their use carefully.

Dr. Parmley (San Francisco, California): It has been pointed out that there is an interaction between the angiotensin-converting enzyme (ACE) inhibitors, particularly captopril, and nonsteroidal anti-inflammatory drugs. Part of its action may be via prostaglandin production at least in cases of hypertension and perhaps also in congestive heart failure. Some NSAIDs may in fact attenuate the effects of captopril as an ACE inhibitor.

Speaker: Your results confirming an increase in plasma renin activity (PRA) in the symptomatic group of patients treated with diuretics are not particularly astonishing. Can you speculate why this was not the case in the asymptomatic group of patients? One would expect PRA to rise with or without diuretics.

Dr. Benedict (Galveston, Texas): I would like to preface my comments by saying that they are speculative. My only explanation for the fact that we did not find a rise in the renin-angiotensin mechanism in asymptomatic patients, at which we were surprised, is that our prevention trial patients were not on any treatment even though they had ventricular dysfunction. If all the changes in the renin-angiotensin system as measured by an increase in PRA were indeed related to the use of diuretics, then we would not find a change. An important qualifier is that the data presented are one-time measurements taken at the time of enrollment of these patients. The study is still being conducted and we are performing serial measurements on these patients to determine whether PRA increases as time progresses, even though they may not be receiving diuretics.

Dr. Jestdal (Norway): In your experiments venous blood samples were used for analysis. Therefore the effects of local release from the forearm muscles and subcutaneous tissues were being studied. I would recommend the use of arterial blood specimens for these studies.

Dr. Benedict: I agree that the measurement of arterial values is very important. However, I would like to point out that arterial blood samples are far more important for the assessment of sympathetic nervous system function, but may not be that important for measurement of PRA. What has to be kept in mind is that when a study involves 6,500 patients it is difficult to take arterial measurements in all the subjects; therefore, for practicality and convenience, we have continued to use venous measurements in this study.

Dr. Forfar: Arterial blood sampling presents problems because it reflects predominantly what has occurred in the lungs, and the lungs are a major source of catecholamine spillover. Therefore, I do not think there is any ideal place for sampling for this sort of study involving large numbers of patients.

Speaker: You mentioned briefly the afferent limb in the baroreceptor reflexes. Would you elaborate on this and say something about your personal point of view regarding the significance of this baroreceptor in the patient with heart failure?

Dr. Forfar: We are probably at the threshold of an explosion of interest and understanding of just what these changes in baroreceptor activity may mean. I think that recent data suggesting that the changes may be reversible relatively quickly are interesting, and I think that has very important implications regarding what we believe to be actually occurring within the baroreceptor system; is it a degeneration or a functional adaptation of the baroreceptors? I think that the fact that the baroreceptors seem to recover fairly quickly implies that there is not a major structural change. In relation to the significance or perhaps the prognostic significance of this, one has to keep an open mind. Data from Rivero and Schwarz suggest that it may be important. Flat baroreceptor responses are disturbing prognostically, and one of the problems for which we do not have adequate answers is predicting prognosis in heart failure and predicting those patients who are going to die suddenly in an unexpected way unrelated to pump failure. I think it is one of many areas that need to be intensively studied.

Dr. Hori (Japan): In relation to the previous question to Dr. Forfar, I would like to know his opinion about the actual mechanism of impairment of the sensitivity of the baroreceptor in early heart failure. It is known that digitalis, an adenosine triphosphatase inhibitor, may restore the sensitivity of the baroreceptors. Do you have any explanation, or even a speculative mechanism explaining the real cause of the impaired sensitivity of baroreceptors?

Dr. Forfar: No, and I am not sure that speculating on mechanisms of desensitization is particularly helpful at this stage of our understanding. It is more important that we work out the time course, the speed of change of any adaptation and the speed of reversal of these changes. It may be possible pharmacologically to reverse stunned baroreceptors. I do not, as yet, have a clear concept of what is actually occurring at the level of the receptor. I think we must await further information in order to understand this; however, I do not think that it is a degeneration of the receptor. I doubt this because I think it is incompatible with the data suggesting fairly quick reversal of reflex function following, for example, cardiac transplantation.

Dr. Parmley: It is known that patients' symptoms frequently have little relationship to ejection fraction. Therefore in your symptomatic and asymptomatic patients, Dr. Benedict, a tremendous overlap in terms of ejection fractions could probably be found. If you looked at symptomatic patients with the same ejection fractions, did you find the same thing in the treatment group as in the placebo-treated group? In other words, is there anything in relation to symptoms that reflects the treatment?

Dr. Benedict: That is a very good question, but as it stands now the study is ongoing and the codes for placebo and treatment groups have not been broken. Therefore, we do not know which patients in the trial are actually in the placebo group or receiving the drug. The data presented are the entry data when the patients were about to be randomized. From the entry criteria, we only detected a small correlation between ejection fraction measurements and the various neurohumoral parameters.

Dr. Barnett (Leicester, United Kingdom): In a study comparing placebo, captopril and frusemide, in postinfarction patients who had dilated ventricles but were asymptomatic, there was a suggestion that after a year, those on frusemide and placebo had an increase in ventricular size and those on captopril did not. It would tend to indicate that, even though an effect on renin activity in the development of this sort of asymptomatic group cannot be measured, captopril was having an effect. Are you familiar with that particular study?

Dr. Benedict: If I am not mistaken, those data were presented by Mark Pfeffer's group from Brigham.[1] The basis of that study is now the SAVE study that I mentioned which is ongoing in the United States and is looking at the efficacy of ACE inhibitors on preventing ventricular dilatation in postmyocardial infarction patients. Our study does not involve patients following acute myocardial infarction; in fact, we wait for a 30-day period or longer before the patients are enrolled. How the findings from that study pertain to these findings are not known, specifically because our patients, at least in the treatment group, are on multiple drug therapy including digitalis, diuretics and nitrates. What is clear is that at least in the prevention trial where the patients are not on any drug therapy, we do not see a change in PRA. How that will now relate to alteration in left ventricular function and onset of symptoms remains to be seen.

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Adrenergic Receptor Responsiveness and Congestive Heart Failure

Gary L. Stiles, MD

Our knowledge and understanding of the structure, mechanism of action and regulation of receptor-adenylate cyclase systems have increased dramatically in the last few years. A family of receptors (including the β-adrenergic receptors) and guanine nucleotide regulatory proteins (G proteins) have been purified and cloned. Structure-function studies are beginning to provide insight into how the various components of the transmembrane signaling apparatus interact to promote alterations in the activity of the effector systems. Much effort has been devoted to understanding how various pathophysiologic conditions, such as ischemia or congestive heart failure, and the therapeutic methods used to treat such conditions perturb or regulate receptor systems. It has become abundantly clear that such regulation does occur but is not restricted to simple alterations in receptor number, and may well involve covalent modification (phosphorylation) of receptors or alteration in the ability of receptors to interact with G proteins. In addition, regulation of the quantity or functionality of the various G proteins and the catalytic unit of adenylate cyclase itself appear to occur. For example, recent evidence suggests that congestive heart failure in humans is associated with a decreased number of β-adrenergic receptors as well as an increased quantity of the inhibitory G protein (G_i). These alterations may provide important insight into how to develop new therapeutic methods. Mechanisms generally responsible for transmembrane signaling, how the components are regulated by pathophysiologic conditions, and drugs used to treat disease states are discussed in detail.

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The endogenous catecholamines are known to regulate physiologic processes as a consequence of their ability to interact with specific membrane-bound receptors such as the α/β-adrenergic receptors.[1] After the binding of agonists, such as epinephrine or norepinephrine, to β receptors, a series of protein interactions ensue that result in an increase in the concentration of intracellular cyclic adenosine monophosphate (cAMP). cAMP is known to be the second messenger for most of the β receptor-mediated actions. The study of transmembrane signaling systems in general has attracted wide attention on account of their central role in modulating cellular function in all systems studied to date. Beta-adrenergic receptor systems have attracted the most attention for several reasons. First, these receptors are present in all cells studied. Second, the coupling of these receptors to their effector system (adenylate cyclase) is well established and much is known concerning the components of the system, thus permitting detailed studies of mechanisms involved in this coupling. Third, the activation or inhibition of β receptors by endogenous catecholamines or therapeutically administered drugs has obvious and important clinical relevance to a wide range of human diseases such as congestive heart failure (CHF), ischemic heart disease and hypertension. Therefore, it would be of benefit to understand the mechanisms by which agonists promote the transmembrane signal that results in changes in cAMP and cellular metabolism. Similarly, it is of critical importance to understand how chronic activation of receptors by elevated concentrations of endogenous catecholamines such as occurs in CHF or consequent to administered β agonists can regulate the various components and interactions of the components of hormone-sensitive adenylate cyclase systems.[1-3] Only through a thorough understanding of the different mechanisms by which transmembrane signaling systems function and the ways in which they are regulated can logical therapeutic methods be elucidated.

The aim of this brief review is to enumerate the components of hormone-sensitive adenylate cyclase systems, to describe how transmembrane signaling occurs and address the question of what happens to these systems under conditions of high catecholamine drive.

COMPONENTS OF HORMONE-SENSITIVE ADENYLATE CYCLASE SYSTEMS

Adenylate cyclase systems are composed of at least 3 distinct integral membrane protein components (Fig. 1). The first comprises the receptors, such as the β-adrenergic receptor or the α_1-adenosine receptor, which recog-

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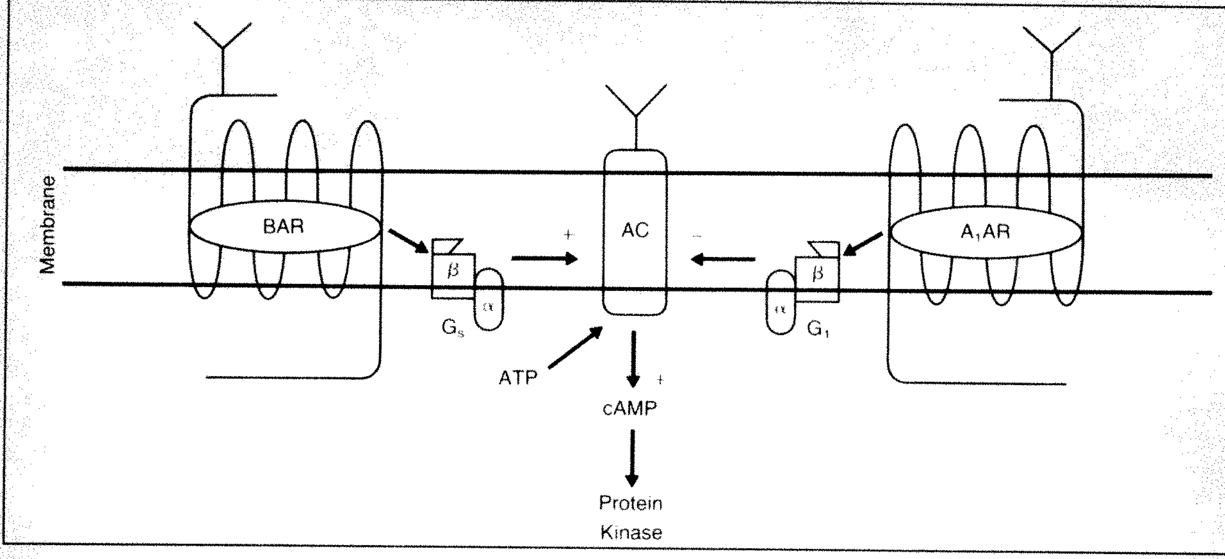

FIGURE 1. Model of receptor-mediated transmembrane signaling. This model demonstrates a typical stimulatory receptor—the β-adrenergic receptor that is coupled to the stimulatory G protein (G_s). The β-adrenergic receptor (BAR) is shown with its transmembrane spanning regions and its carbohydrate component (Y) which is on the external side of the membrane. The G_s protein is shown as its heterotrimeric form with the α and β subunits labeled. The smallest subunit is the γ subunit. The catalytic unit of adenylate cyclase (AC) is shown as a transmembrane protein with its external carbohydrate chain(s). Also shown is a typical inhibitory receptor—the A_1-adenosine receptor (A_1AR) which acts through the inhibitory G_i protein to suppress adenylate cyclase. Adenosine triphosphate is shown being converted to cyclic adenosine monophosphate (cAMP) where it can then activate protein kinase A.

nize and bind their appropriate agonist ligand and then interact with the second components of the system—the guanine nucleotide-binding protein–stimulatory G protein (G_s) and inhibitory G protein (G_i), respectively. The G proteins represent an increasingly large family of coupling proteins that activate or inhibit the activity of a wide range of effector systems, such as adenylate cyclase, phosphoinositol metabolism, phosphodiesterases and K^+ channels. The third component of the system of interest is the enzyme adenylate cyclase. Recent studies suggest that the catalytic moiety of adenylate cyclase is a transmembrane protein, which in addition to being able to catalyze the conversion of adenosine triphosphate to cAMP, may also be able to act as an ion channel or transporter system.[4] There are now known to be multiple forms of both G_s and G_i in cells, but the functional importance of these various isoforms or alternate splices remains largely unknown.[4,5]

There are striking structural similarities among all the G proteins. They are all heterotrimeric in nature, having single α subunits with molecular weights ranging from 39,000 to 53,000, β subunits of molecular weight 35,000 to 36,000 and a γ subunit of molecular weight, approximately 8,000 to 10,000. G protein specificity in terms of receptor interactions and possibly effector interactions resides in the α subunit because the $\beta\gamma$ subunit appears relatively interchangeable among the various α subunits.[4] There are exceptions to this generalization but those details are beyond the scope of this review.

The α subunit contains the guanosine triphosphate-binding site as well as the intrinsic guanosine triphosphatase activity that is responsible for deactivating the guanosine-liganded phosphate α subunit by promoting the hydrolysis of guanosine triphosphate to guanosine diphosphate.[4] The subunits are also the substrates for the various toxin-catalyzed adenosine diphosphate ribosylation reactions that occur. The various domains of the α subunit are now beginning to be studied in detail.[6]

RECEPTOR-EFFECTOR ACTIVATION PATHWAYS

Adenylate cyclase systems in the heart, as in other tissues, are vectorial in that the amount of cAMP generated is related to a number of factors, including the relative activity of G_s (as activated by stimulatory receptors) and G_i (activated by inhibitory receptors), the quantity and functionality of the catalytic unit of adenylate cyclase, and the relative activity of specific phosphodiesterases that are acting to degrade cAMP. This makes attempts to implicate either qualitative or functional alterations of any one component of the system, assessed in vitro, as the cause of altered sensitivity or functionality, in vivo, fraught with danger. This is particularly relevant when it is remembered that receptor systems are amplification systems, in which one receptor can activate multiple G_s proteins which in turn activate the catalytic unit to convert more than one molecule of adenosine triphosphate to cAMP. In addition, there are a number of receptors in the heart that activate G_s and subsequently increase cAMP concentration, including β receptors, glucagon receptors and vasoactive intestinal protein receptors. Similarly, there are a number of receptors that activate G_i and thus decrease adenylate cyclase activity, including muscarinic receptors and A_1-adenosine receptors.[7] Thus, even if a change in catecholamine-mediated myocardial contractility were consequent to alterations in myocardial

TABLE I Modes of Regulation

Changes in receptor number
Covalent alterations in receptor
Changes in receptor G protein coupling
Changes in G protein quantity
Changes in G protein functionality
Changes in G protein—catalytic unit interaction
Alterations in catalytic unit activity

TABLE II Examples of Particular Modes of Regulation

Parameter	Pathophysiologic Condition
Receptor number	Ischemia, desensitization, congestive heart failure
Receptor structure	Desensitization
Receptor-G protein coupling	Desensitization, congestive heart failure
G protein quantity	Congestive heart failure, desensitization
G protein functionality	Desensitization

cAMP concentrations in CHF, it could still be consequent to alterations in any of these described components of the system. Thus, if the overall aim is to understand the mechanisms involved in altered transmembrane signaling in CHF, each of the various components (receptors, G proteins, catalytic unit) must be studied individually and together.

The biochemical mechanisms and interactions of the various components required to activate or inhibit adenylate cyclase have been described in detail elsewhere[1,4,8] and a detailed description will not be provided here. Only those aspects that are pertinent to the current discussion will be delineated in detail.

POTENTIAL MECHANISMS FOR ALTERATIONS IN TRANSMEMBRANE SIGNALING

Investigations over the past 10 years or so have demonstrated that each of the components of hormone-sensitive adenylate cyclase systems can be altered either quantitatively or functionally, or both, in a variety of different model systems.[1,3] Not all changes are seen in any one system, and information concerning transmembrane signaling systems in ventricular myocardial tissue has only slowly been elucidated because of a variety of technical difficulties in working with myocardium and tissue acquisition problems. Table I lists examples of modes of regulation that have been described, although not all these changes have so far been described in the heart. Alterations in receptor number, e.g., are not limited to the stimulatory β receptor but can also involve changes in inhibitory receptors, such as the A_1-adenosine receptor or the muscarinic receptor.[9] Similarly, changes in G proteins can involve alterations in G_s, G_i, or both of these proteins, in selected model systems. Table II lists some examples of particular modes of regulation described in the published reports.[3]

Recent studies have documented that a number of changes occur in the adenylate cyclase system in the heart when CHF is present.[10-12] These include decreases in the number of β-adrenergic receptors and uncoupling of β-adrenergic receptors from G_s, i.e., less effective activation of G_s for a given agonist stimulation and consequently a decrease in adenylate cyclase activity for a given catecholamine stimulation. Finally, and most recently, it has been demonstrated by 2 independent groups that the quantity of the inhibitory G protein G_i is increased in myocardial tissue from patients with CHF.[11,12]

All of these alterations could help explain the decreased sensitivity of the heart to catecholamines in CHF. However, it should be pointed out that a causal relation between these alterations and the decreased contractile response in the heart has not been documented.

Because the model that might most accurately describe the β-receptor system in the heart during CHF is catecholamine desensitization, a description of what is now known in chronic heart failure will be discussed in light of what is known to occur in other β-receptor systems after chronic agonist exposure. This is obviously an oversimplication because CHF and myocardial contractile insufficiency constitute a multifactorial process.

The first general assumption is that the hormone-sensitive adenylate cyclase system of the heart in CHF is less responsive to catecholamine stimulation in terms of cAMP generation. However, not all stimulatory agonists, such as histamine, demonstrate such a subsensitivity.[13] Many lines of evidence now suggest that subsensitivity to catecholamines does occur. This pattern of altered sensitivity to catecholamines is suggestive of a homologous type of desensitization. However, other data concerning the transmembrane signaling apparatus in CHF (i.e., increased G_i protein) would not fit this pattern of desensitization. Therefore, it is worthwhile describing the 2 types of desensitization generally recognized.

Agonist-specific or homologous desensitization is usually defined as a decrease in adenylate cyclase responsiveness to a single agonist after chronic exposure to that agonist. In contrast, heterologous desensitization occurs when the responsiveness of a number of receptor-mediated agonists or nonreceptor activators of adenylate cyclase, such as guanosine triphosphate or sodium fluoride, are decreased after exposure to a single agonist.[1,3] However, these 2 processes may not be mutually exclusive, and heterologous desensitization can occur in addition to homologous desensitization, particularly if agonist exposure is prolonged.[3] This makes analysis of a system difficult unless one can control the external environment of cells, which obviously cannot be achieved in patients with CHF.

Homologous desensitization: There are several likely steps in the process of homologous desensitization that all appear to be receptor-specific in nature. The first phase appears to be a rapid uncoupling of the receptor from activation of adenylate cyclase. This process occurs rapidly (in minutes) in the model systems studied. The second phase is a rapid sequestration of the receptor away from the cell surface into a "compartment" that is less accessible to hydrophilic radioligands. These receptors can be

TABLE III Human Congestive Heart Failure

What do we not know?
- Are any of the described phenomena of receptor mechanisms important or are they epiphenomena?
- Are the receptors covalently modified?
- What role does β-adrenergic receptor kinase play?
- Is the catalytic unit modified quantitatively or qualitatively?
- Are increased G_i proteins important?
- Is the inhibitory side of the adenylate cyclase system enhanced? (increased sensitivity to adenosine)

detected through the use of hydrophobic antagonist ligands. The third phase is true down-regulation in which receptor number is truly decreased in the cell. Under these circumstances receptors cannot be detected with any radioligands. This phase of regulation is associated with a more prolonged exposure to agonists than either of the first 2 phases. Recent evidence links the phosphorylation of the β-adrenergic receptor with the process of desensitization although a true causal relation has not yet been proved.[3]

A major step forward in elucidating potential mechanisms involved in homologous desensitization was the discovery and characterization of a new receptor-specific kinase by Benovic et al.[14,15] This kinase has been called the β-adrenergic receptor kinase, although it is now known that it can phosphorylate other integral membrane receptors. This kinase is different and distinct from other kinases, such as the cAMP-dependent protein kinase or protein kinase C. The most interesting property of β-adrenergic receptor kinase is that it preferentially phosphorylates the agonist-occupied receptor rather than an antagonist or unoccupied receptor. This raises the prospect that in vivo phosphorylation of the agonist-occupied receptor may play a direct role in the desensitization process. There is compelling circumstantial evidence that this may be the case. First, the phosphorylated receptor under the appropriate in vitro conditions displays an 80% decrease in its ability to interact with G_s (uncoupled). Second, the time course for phosphorylation of the β-adrenergic receptor in intact cells parallels the time course of desensitization.[3] Third, β-adrenergic receptor kinase displays wide tissue distribution.[3] Finally, the sequestration of phosphorylated receptors into the cell is subsequently associated with their dephosphorylation and recycling back to the cell membrane.

Further studies are needed to document a cause and effect relation between phosphorylation and desensitization. In addition, homologous desensitization is not thought to be a cAMP-mediated event, i.e., elevated concentrations of cAMP without receptor activation and consequent increased protein kinase A activity do not mimic catecholamine-induced desensitization.

Heterologous desensitization: In contrast, heterologous desensitization may involve multiple pathways that involve both receptor protein changes as well as alterations in the other components of the adenylate cyclase systems. This form of desensitization usually results from a more prolonged exposure to agonists and the process proceeds at a slower rate. In contrast to homologous desensitization, heterologous desensitization can be directly induced by increases in cAMP concentrations in some systems.[3] Thus, administration of stable analogs of cAMP to cells can totally mimic the phenomenon of catecholamine-induced desensitization in some model systems. This suggests that activation of protein kinase A may be a mediator of some forms of desensitization. Various studies have documented modifications of each of the components of the hormone-sensitive adenylate cyclase system in various models of heterologous desensitization. Beta-receptor phosphorylation has been demonstrated to occur in intact cells after agonist exposure or by direct phosphorylation of the purified receptor by both protein kinase A and protein kinase C, singly or in combination. The direct role of these phosphorylations in the desensitization process remains to be elucidated.

Modifications of G proteins: Modifications of the G proteins both in terms of quantity and functionality have been described in various forms of desensitization.[3,9] A growing number of studies suggest that the quantity of G_s and G_i can be altered by chronic agonist activation of either stimulatory and inhibitory receptor systems coupled to adenylate cyclase.[3,9] The mechanisms responsible for this type of regulation need to be elucidated. Thus, alterations in the relative stoichiometry of G_s to G_i could account for the process of desensitization. Adenylate cyclase could become less sensitive to catecholamine stimulation either by decreasing G_s or by increasing G_i. Both phenomena have been described in various cell models.[3,9]

Although G_i has been phosphorylated in vitro, there is no evidence that phosphorylation of G_s or G_i plays a physiologic role in regulating adenylate cyclase systems.[2,3]

Unresolved areas: There is very little information on whether the final component of the adenylate cyclase system is regulated in the desensitization process. It would not be surprising if it were, because heterologous desensitization often demonstrates a diffuse loss of response to stimulatory agents. No tools have been described to quantify the catalytic unit precisely, so it is unknown whether it is modulated quantitatively. Protein kinase A can phosphorylate the purified catalytic subunit, but whether this process occurs in vivo or is a method of regulation in vivo is unknown.[3]

From this brief review of the modes of regulation that can occur during the desensitization process, it is clear that much remains to be learned concerning potential mechanisms involved in the subsensitivity of the heart to catecholamines. What then are the areas that remain unknown in the β-adrenergic receptor-adenylate cyclase system in the heart in CHF? Some of these are listed in Table III. Are any of the changes so far observed in the β-adrenergic receptor adenylate cyclase system of the heart important mechanisms in the suppressed contractility or are they an epiphenomenon? Although it makes intuitive sense that they are important, many other factors must also be important. To the extent that this transmembrane signaling system is important or causal, what then remains to be learned includes whether the remaining β-adrenergic receptors in the membrane are covalently modified and whether β-adrenergic receptor kinase plays a significant role in the process of desensitization. It is unclear whether the catalytic unit itself is modified in CHF. Although early data from Hershberger and Bristow[10] suggested that it was not, more recent information indicates that its activity may be decreased.

The intriguing finding that the G_i protein concentration is increased in hearts from patients with CHF suggests that there may be a decreased basal adenylate cyclase activity or an enhanced receptor-mediated inhibition of adenylate cyclase under the influence of inhibitory agonists, such as acetylcholine or adenosine. An increased G_i concentration could manifest itself as a relative desensitization or refractoriness to stimulatory hormones. There is a need for further investigation of the inhibitory side of the adenylate cyclase system, including detailed studies of the G proteins. Additionally, current methods allow the assessment of which types of the G_i protein (αi1, αi2 or αi3) are increased in heart failure. It will be important to learn which G_i subtypes are in the heart and which are regulated. Pertussis toxin labeling does not differentiate between the 3 forms of G_i or G_o (a G protein abundant in brain and other tissues, the function of which is unknown) because all are substrates for $[^{32}P]$NAD labeling.

DESIGNING THERAPY BASED ON MECHANISMS

If the changes observed in the β-adrenergic receptor/adenylate cyclase system are important and a consequence of catecholamine desensitization, β-receptor antagonism has theoretical benefit. Care must be exercised in administering β blockers to patients with CHF. There have been several studies to suggest that β blockers may improve the condition of some patients with CHF.[16,17] Another potential approach for therapy would be an attempt to block the process of desensitization from within the cell. Thus, if β-adrenergic receptor kinase or other enzymes mediate desensitization, specific inhibition of these enzymes may be useful clinically.

The newer classes of positive inotropes or analogs derived from them may be useful and have theoretical advantages. It has recently been demonstrated that positive inotropes display at least 3 distinct mechanisms of action that have direct impact on the relevant components of the adenylate cyclase system.[18,19] Compounds such as milrinone and sulmazole are phosphodiesterase inhibitors that block cAMP degradation and enhance contractility through a protein kinase A mechanism. In addition, it has been demonstrated that these compounds are specific antagonists of A_1-adenosine receptors and also inhibit the activity of the G_i protein.[14,19] The A_1-adenosine receptor that is present in the heart is known to mediate inhibition of adenylate cyclase activity and to suppress contractility. Thus, antagonizing a receptor that mediates decreased contractility may produce great therapeutic benefit.

There is an increased concentration of G_i in the heart, and if it contributes to suppressed cAMP, then blockade of G_i activity would increase cAMP and thus contractility. If adenosine-mediated inhibition of adenylate cyclase is also enhanced, then blockade of A_1 adenosine receptors would also enhance contractility. Thus, direct pharmacologic manipulation A_1-adenosine receptors and G_i by new agents which specifically act on each of these sites may be a fruitful area of research.

CONCLUSION

Multiple changes in the β-adrenergic receptor/adenylate cyclase system have been described in CHF. Their etiologic role in the perpetuation or exacerbation of CHF requires further study. Much remains to be learned concerning the mechanisms responsible for the observed alterations. To the extent that the adenylate cyclase system is important in the pathophysiology of CHF, it is beneficial to understand the basic biochemical mechanism involved and to design new therapies based on these mechanisms.

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Cardiac Beta-Adrenoceptor Regulation and the Effects of Partial Agonism

David B. Barnett MD, and Xianyou Lu, MD

The in vivo effects of xamoterol on the regulation of rat cardiac β adrenoceptors were investigated. Rats were implanted subcutaneously with osmotic minipumps and exposed to the following treatment regimens: (1) subcutaneous infusion of saline (control), isoprenaline or xamoterol for 6 days, (2) subcutaneous infusion of isoprenaline with co-administration of xamoterol for various periods up to 96 hours, and (3) subcutaneous infusion of xamoterol for up to 96 hours after previous treatment with isoprenaline for 72 hours. Xamoterol did not induce β-adrenoceptor down-regulation after short-term (72-hour) or long-term (6-day) infusions. When co-administered with isoprenaline xamoterol did not affect the rate or extent of down-regulation induced by isoprenaline alone. In addition, recovery of β adrenoceptors down-regulated by isoprenaline treatment was not influenced by xamoterol treatment. In all studies, doses of xamoterol were equivalent to those producing full functional responses to the drug in vivo.

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It is generally accepted that chronic agonist stimulation of β_1 adrenoceptors produces desensitization and is usually associated with a reduction in tissue receptor density (down-regulation) or uncoupling of the receptor from adenylate cyclase, or both.[1] Conversely chronic treatment with β-adrenoceptor antagonists may induce an increase in receptor density (up-regulation) and increase responsiveness.[2] Thus, attempts at chronic treatment of heart failure with the β_2 adrenoceptor agonist pirbuterol have been unsuccessful because of rapid development of receptor desensitization.[3] Furthermore, in chronic heart failure, β-adrenoceptor down-regulation has been demonstrated in hearts removed from transplant recipients presumably related to the chronic sympathetic nervous stimulation characteristic of this condition.[4]

It is possible that the β-adrenoceptor selective partial agonist xamoterol may be of particular use in heart failure, being less likely to induce receptor down-regulation or reduce responsiveness during chronic treatment. It may also protect cardiac β adrenoceptors from "adverse" regulatory influences of excessive noradrenergic discharge present during the development of heart failure.

Because of the clinical interest in xamoterol, we have investigated the effects of this agent on regulation of rat cardiac β adrenoceptors in vivo. The experiments were designed to answer the following questions: (1) Does chronic treatment with xamoterol induce cardiac β-adrenoceptor down-regulation compared with similar treatment with the full agonist isoprenaline? (2) Does co-administration of xamoterol with isoprenaline influence the rate or extent of down-regulation or recovery of the cardiac β adrenoceptors induced by the full agonist isoprenaline?

METHODS

Using osmotic minipumps (Alza, Palo Alto, California) implanted subcutaneously in rats the following treatment regimens were employed: (1) subcutaneous infusion of saline (control), isoprenaline (40 μg/kg/hour) or xamoterol (600 μg/kg/hour) for 6 days; (2) subcutaneous infusion of isoprenline (40 μg/kg/hour) with co-administration of xamoterol (600 μg/kg/hour) for various periods up to 96 hours; (3) subcutaneous infusion of xamoterol (600 μg/kg/hour) for up to 96 hours after prior treatment with isoprenaline (40 μg/kg/hour) for 72 hours. Xamoterol treatments in regimens 2 and 3 were preceded by a single intraperitoneal priming injection of 0.1 mg/g of the drug.

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At the end of the treatment periods, the rats were killed and blood was sampled for isoprenaline and xamoterol plasma concentration measurements. Hearts were removed and myocardial membranes prepared using standard methods.[5] Receptor densities (β_{max}) for total β adrenoceptors and β_1 and β_2 subtypes were assessed from saturation analysis of ^{125}I-pindolol binding as previously described.[6]

RESULTS

Isoprenaline: The infusion of isoprenaline for 72 hours reduced total β-adrenoceptor B_{max} by approximately 40 to 50%. No further down-regulation was induced by 6 days' treatment. The relative proportions of the β-adrenoceptor subtypes (65 to 70%) were not affected by chronic isoprenaline treatment. However, during short-term isoprenaline infusions, β_2 adenoceptors were down-regulated more rapidly and to a greater extent (maximal down-regulation 60% at 24 hours) than β_1 adrenoceptors (maximal down regulation 45% at 48 hours). Recovery of down-regulated β adrenoceptors was observed in rats treated initially with isoprenaline for 72 hours. After removal of the minipumps, the rats were allowed to recover and then killed at various time intervals up to 96 hours. β_1 adrenoceptors returned at a slower rate to the control state than did β_2 adrenoceptors (full recovery at 48 and 96 hours for β_2 and β_1 subtypes, respectively).

Xamoterol: Infusion of xamoterol alone for any time period (72 hours to 6 days) did not affect β-adrenoceptor density. In addition, the relative proportions of the β-adrenoceptor subtypes were unchanged by xamoterol treatment. This indicates that the β_1 selective partial agonist did not cause down-regulation of β_1 adrenoceptors associated with a compensatory increase in β_2 adrenoceptors accounting for the unchanged overall B_{max} value.

Xamoterol and isoprenaline: When co-administered with isoprenaline, xamoterol did not affect the rate or degree of down-regulation induced by isoprenaline. In addition, recovery of down-regulated receptors was not influenced by subsequent treatment with xamoterol.

Plasma concentrations of xamoterol measured at the end of all treatment periods (100 to 300 nmol/liter) were similar to those producing full functional responses in rat heart in vitro and in vivo, suggesting full receptor occupancy for the partial agonist during the infusion experiments.

CONCLUSIONS

In this animal model, xamoterol does not induce adrenoceptor down-regulation in short-term (72 hours) or long-term (6 days) infusion studies using doses equivalent to those producing full functional responses to the drug in vivo and in vitro. Xamoterol, when co-administered with isoprenaline, does not affect the rate or extent of down-regulation induced by the full agonist. In addition, recovery of down-regulated β adrenoceptors after isoprenaline treatment is not influenced by xamoterol.

These results have important implications for the use of xamoterol in the therapy of chronic heart failure. In particular, it seems that tachyphylaxis in response to the inotropic effects of xamoterol during long-term treatment would be unlikely. The present experiments, however, do not indicate a "protective" effect of xamoterol when the cardiac β adrenoceptors are exposed to strong stimulation by a full agonist. This may be related to the artificial nature of the stimulus used in the present model (high-dose isoprenaline infusion) as well as the relative doses of the 2 agents. Further studies are currently underway to explore these possibilities.

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Interrupting the Adaptive Changes in Congestive Heart Failure

Wolfram Kupper, MD

Circulating plasma concentrations of norepinephrine, renin, angiotensin and vasopressin are increased in congestive heart failure. By increasing ventricular afterload, heart failure is further worsened, which in turn—in a vicious cycle—stimulates neurohumoral vasoconstrictor mechanisms. Furthermore, because of the compensatory but excessive stimulation of the sympathomimetic system, a down-regulation and desensitization particularly of the myocardial β_1 receptors and depletion of myocardial catecholamine occurs in chronic heart failure. These defects may be restored toward normal by interventions that attenuate the activity of the sympathetic nervous system. A direct approach to modify the excessive vasoconstriction is to administer systemic vasodilator drugs, but despite favorable short-term effects, tolerance developed to most of these drugs during long-term treatment. One reason for the loss of effectiveness is the reflex activation of the sympathetic system, which increases vasoconstrictor hormone concentrations. Activation of the renin-angiotensin system can be modified effectively by angiotensin-converting enzyme inhibitors that have shown favorable responses in patients with chronic heart failure. Beta-blocking agents interfere with endogenous sympathetic activation and have produced beneficial effects in patients with congestive cardiomyopathy. Long-term treatment is associated with upregulation of the number of β receptors and an improved responsiveness to catecholamines. Owing to the negative inotropic effects of β-blocking agents, some of the patients with severe heart failure deteriorated hemodynamically and clinically. Theoretically, it should be advantageous to have a substance that combines protection against excessive β stimulation with a mild inotropic support to prevent cardiac decompensation. This may be achieved by a selective β_1-partial agonist like xamoterol.

(Am J Cardiol 1991;67:20C–22C)

Under normal circumstances, baroreceptors provide a tonic inhibition of the sympathetic nervous system. An acute decrease in cardiac output or arterial pressure decreases baroreceptor activity, which leads to sympathetically mediated vasoconstriction and activation of the vasopressin and renin-angiotensin systems. Several lines of evidence show that baroreceptor function is impaired in patients with heart failure. For example, in normal persons, upright tilt causes venous pooling of blood, producing a decreased filling pressure and cardiac output, which in turn causes reflex vasoconstriction and an increase in heart rate and blood pressure. In patients with congestive heart failure, however, heart rate, arterial pressure and forearm vascular resistance do not alter during upright tilt, which suggests that the sympathetic response to reduced cardiac output is impaired in these patients.[1] Furthermore, plasma norepinephrine and epinephrine concentrations in patients with heart failure do not increase during upright tilt, whereas in control subjects plasma norepinephrine increases by approximately 80%.[2] Thus, in patients with heart failure, the inhibition of sympathetic activity normally provided by baroreceptors is greatly reduced. Activation of the sympathetic nervous system is known to occur early in heart failure; Bayliss et al[3] showed that this activation occurs before onset of symptoms.

ADVERSE CONSEQUENCES OF SYMPATHETIC STIMULATION

The baroreceptor reflex provides a means of compensating for short-term changes in cardiac output. Prolonged activation of the sympathetic nervous system, however—as occurs during congestive heart failure—has 3 major effects which can have deleterious consequences for the patient. Chronic sympathetic activation leads to down-regulation of myocardial β_1-adrenoceptor desensitization and increases afterload, chronic activation of the renin-angiotensin system leads to sodium and water retention, and the decreased cardiac output contributes to the general debilitation of patients with congestive heart failure. Under these conditions, the normally beneficial increases in heart rate and blood pressure produced by the baroreceptor reflex can become disadvantageous (Table I). A chronic increase in heart rate can, particularly in patients with coronary artery disease, produce myocardial ischemia, an increased myocardial oxygen consumption and a reduced diastole. An increase in mean arterial pressure resulting from angiotensin II secretion can both increase impedance and decrease ejection fraction. Increased contractility increases stroke volume and ejection fraction, but this is at the expense of worsening arrhyth-

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TABLE I Effects of Sympathetic Activation in Heart Failure

- Beneficial
  - Tachycardia: cardiac output increases
  - Arterial constriction: mean arterial pressure increases
  - Venous tone increases: end-diastolic volume increases
  - Renin stimulation: end-diastolic volume increases, mean arterial pressure increases
  - Myocardial hypertrophy: cardiac output increases
  - Contractility increases: stroke volume increases, ejection fraction increases
- Detrimental
  - Myocardial oxygen consumption increases, diastole decreases
  - Impedance increases, ejection fraction decreases
  - Preload increases, wall stress increases
  - Impedance increases, ejection fraction decreases
  - Compliance increases, filling pressure increases
  - Arrhythmias increase

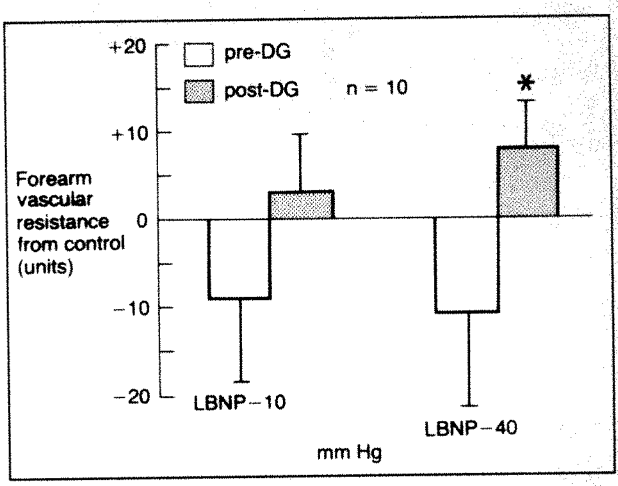

FIGURE 1. Forearm vascular responses to lower body negative pressure (LBNP) in patients with congestive heart failure, before (pre) and after (post) treatment with digitalis (DG).

mias, as can occur, e.g., during administration of inotropic agents such as catecholamines or phosphodiesterase inhibitors. A vicious cycle therefore exists in which neuroendocrine responses to ventricular dysfunction lead to increased peripheral resistance and afterload, causing a further deterioration in ventricular function.

POSSIBLE APPROACHES TO RESTORING NORMAL BARORECEPTOR FUNCTION

It appears that the diminished baroreceptor activity that occurs during heart failure does not result from structural changes in the receptor itself, because normal reflex activity is restored within 2 weeks of cardiac transplantation. Thus, the most effective means of interrupting the vicious cycle previously described are cardiac transplantation or the use of a left ventricular support device. However, these physical interventions clearly are practical or appropiate only in a limited number of patients.

Pharmacologic approaches to restoring baroreceptor function involve reducing the load on the heart, increasing myocardial contractility or changing the ionic environment of the receptor. For example, digitalis inhibits membrane sodium-potassium adenosine triphosphatase and Ferguson et al[4] found that digitalis normalizes the forearm vascular response to lower body negative pressure in patients with congestive heart failure (Fig. 1).

The load on the heart can be reduced by treatment with angiotensin-converting enzyme inhibitors, such as captopril. Cody et al[5] studied the vascular responses to cold in patients with congestive heart failure after acute and chronic treatment with captopril. After acute administration of captopril, heart rate and systolic and diastolic arterial pressures did not change when one hand was immersed in iced water for 1 minute. However, when captopril was given chronically, cold stress produced a marked increase in heart rate and blood pressure that was similar to that seen in normal subjects.

The β-adrenoceptor-adenylate cyclase system is markedly altered during heart failure. In advanced disease, the concentration of myocardial β receptors is decreased; this decrease is mainly due to a reduction in the number of β_1 receptors.[6] Moreover, metoprolol and other β antagonists cause up-regulation of myocardial β adrenoceptors and restore the sensitivity of the receptor to agonist stimulation.[7] Down-regulation of β receptors is not due to simple agonist occupancy of the adrenergic receptor, because the affinity of the α adrenoceptor (which is not down-regulated in chronic congestive heart failure) for norepinephrine is only slightly less than that of the β receptor. Changes in the nucleotide-binding regulatory proteins that couple the receptor to adenylate cyclase may be involved. Concentrations of the stimulatory G_s protein are decreased by up to 80% in patients with congestive heart failure[8]; treatment with the angiotensin-converting enzyme inhibitors captopril or lisinopril doubled the concentration of G_s proteins and increased the concentration of β receptors.[8]

Treatment with β-receptor antagonists has benefited some patients with severe heart failure but, because of the negative inotropic effects of these drugs, the condition of others deteriorates. It would be advantageous to combine a weak β_1 agonist effect with protection against the harmful effects of chronic receptor stimulation.

Studies with xamoterol: In rats, treatment with xamoterol did not cause down-regulation of β adrenoceptors,

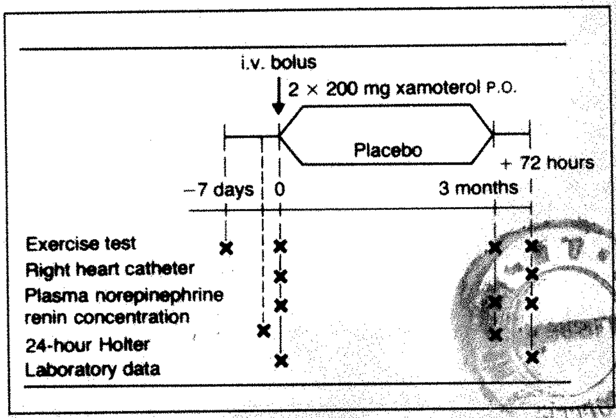

FIGURE 2. Protocol of the study of the effect of xamoterol, 200 mg administered twice daily for 3 months in 30 patients. i.v. = intravenous.

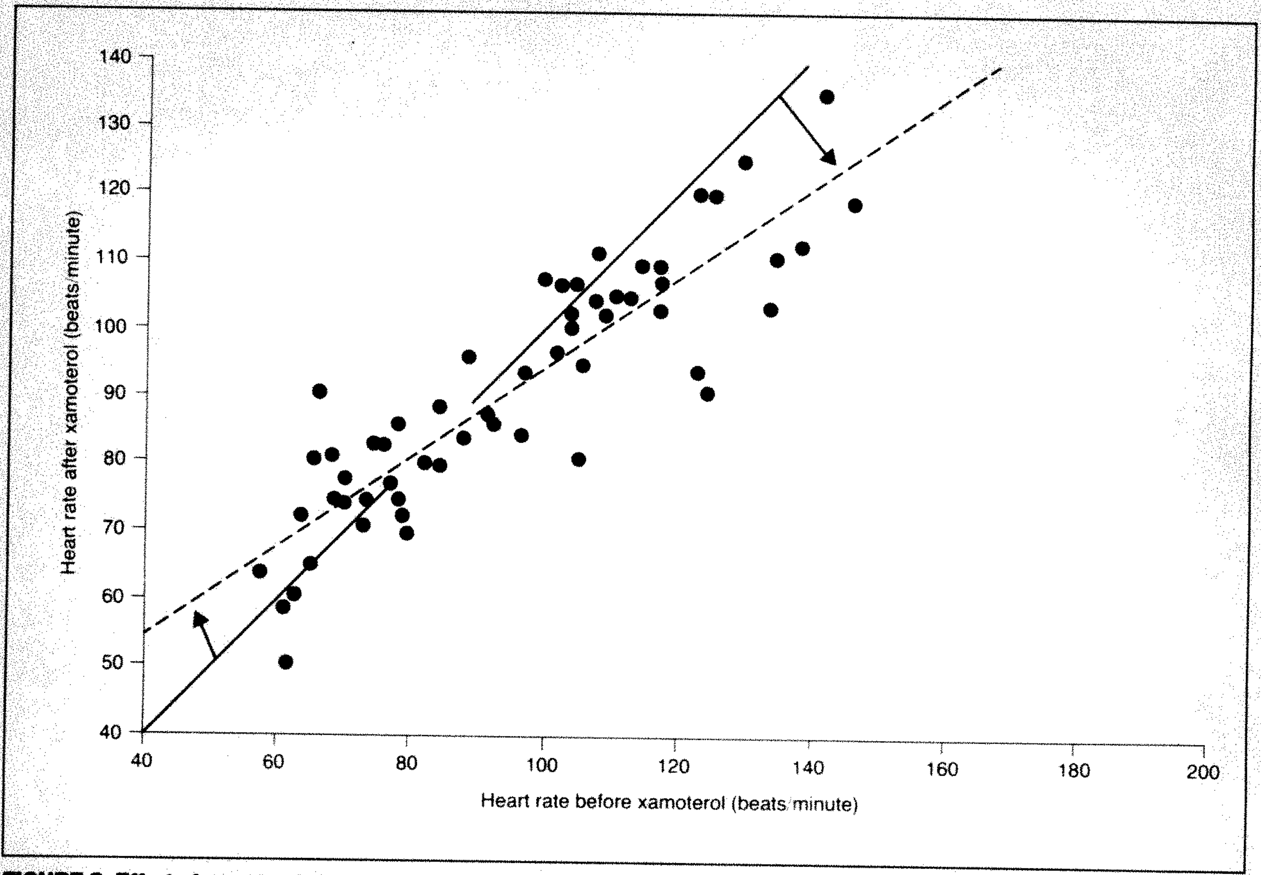

FIGURE 3. Effect of xamoterol, 0.2 mg/kg administered intravenously, on heart rate. Pooled data from values at rest and on exercise. *Solid line*; line of identity; *dashed line*; regression line.

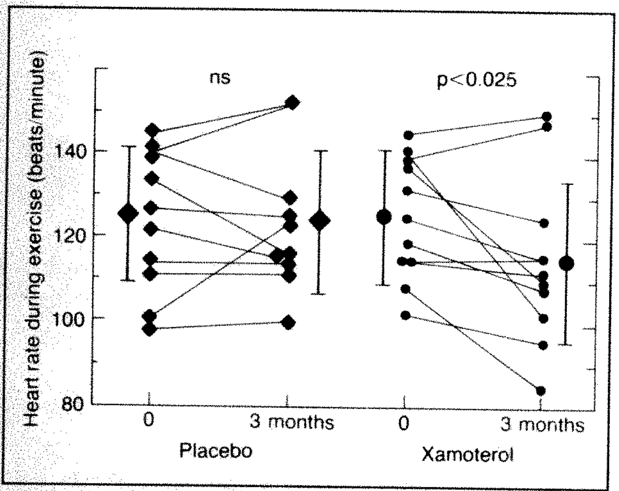

FIGURE 4. Effect of 3 months' treatment with xamoterol, 200 mg administered twice daily, on exercise heart rate. The significant decrease in exercise heart rate seen after acute administration is maintained after long-term therapy, indicating lack of tolerance development.

unlike isoprenaline (see Barnett's report on p 18C of this supplement). A double-blind, randomized, placebo-controlled trial has examined the effects of 3 months' treatment with xamoterol (200 mg twice daily) on hemodynamics in patients with heart failure (Fig. 2). A single intravenous dose of xamoterol, 0.2 mg/kg, produced a decrease in exercise heart rate and a slight increase in resting heart rate (Fig. 3 and 4), and these effects were not altered by 3 months' treatment. These results suggest that (1) in patients at rest, xamoterol has a mild inotropic effect, whereas at times of high sympathetic activity (i.e., during exercise) it has an overall antagonistic effect; and (2) tachyphylaxis is unlikely to occur during chronic treatment with xamoterol.

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Panel Discussion

Dr. Grobecker (Federal Republic of Germany): Dr. Stiles, in view of the excellent experiments of Maisel and co-workers[1] showing that there is an externalization of receptors in guinea-pig hearts and in view of your excellent presentation illustrating that there is an internalization, would you classify coronary heart disease and the failing heart in terms of receptor movements inward and outward?

Dr. Stiles (Durham, North Carolina): I do not think we have any data that tells us whether receptor movements inward and outward are different. As I tried to point out in my talk, I do not know that what we are looking at is in fact a physiologic change in the β receptors; it may all be end-stage disease. I think it is clear that if a cell is continually bathed in catecholamines a refractoriness or tachyphylaxis will be seen. In some systems that occurs without down-regulating β receptors at all; in some systems only covalent changes are seen in the receptor and changes can be seen in the G proteins without any change in β-receptor number at all. In other systems you see down-regulation very quickly, in minutes, and in some cases when the catecholamine stimulation is removed it reverts to normal. I think your point is a good one, although I do not think we can categorize all types of end-stage heart failure into 1 group. I think there are very different types—end-stage heart failure resulting from immunologic disease and viral disease is very probably different to that seen in end-stage ischemic disease where the patient has had 3 or 5 infarcts and has very little functioning muscle left because it has all become fibrotic.

Dr. Grobecker: Regarding uptake by the sympathetic nerves and subsequent release on sympathetic stimulation, is xamoterol or metoprolol taken up in this way? Do you have any evidence for this?

Dr. Barnett (Leicester, United Kingdom): What you are asking is whether xamoterol is a substance for a type 1 uptake mechanism. To my knowledge, no.

Dr. Parmley (San Francisco, California): Years ago we were interested in the effects of glucagon in terms of stimulating cardiac contractility and, following studies in patients, noted that in heart failure it seemed to work less well. This was substantiated in the muscle removed from patients with severe heart failure. What is the mechanism for this decreased responsiveness to glucagon?

Dr. Stiles: The glucagon system has not been looked at in any detail in the heart, but it has been in a variety of other cells including the kidney, and there is some very interesting work from Rich et al[2] looking at glucagon desensitization. They proposed a unique mechanism explaining how desensitization to glucagon occurs as a result of these studies. They found that chronic treatment of liver cells with glucagon induced a tachyphylaxis over about 12 to 24 hours and the mechanism appeared to involve an increase in the G_i protein concentration. This is analogous to what has now been described in the human heart: If you look at only the stimulatory side of the system it looks fairly normal. A little down-regulation of the glucagon receptors was observed, but it was noted that on the inhibitory side of the axis it was markedly enhanced, which was the first time such events were described, and it has subsequently been confirmed by a variety of other researchers. Therefore, we can gather from this that a system can be regulated in ways other than via the receptor. Whether that is analogous to what happens in the human heart I do not know, but increased G_i protein concentration has been observed in the human heart, and it is known that the human heart in congestive failure is refractory to glucagon.

Dr. Kupper (Hamburg, Federal Republic of Germany): Besides the pharmacologic action, one of the other reasons for discontinuing therapy was the side effects seen in our patients.

Dr. Stiles: Yes, they suffered from nausea.

Dr. Forfar (Oxford, United Kingdom): Xamoterol does not prevent agonist down-regulation and presumably this must relate to the concentrations in receptor occupancy of the agonist and partial agonist. What was it in your study?

Dr. Barnett: You are quite right. What I would have liked to have seen would have been that xamoterol co-administered with isoprenaline would have allowed the β_2 adrenoceptor to down-regulate and would have prevented the down-regulation of the β_1 adrenoceptor. The second part of the experiment would have also been predictable in a theoretical sense, the co-administration of xamoterol during receptor recovery, would hopefully have encouraged a more rapid up-regulation recovery of the β_1 receptors. Neither of those things happened, and that may be because it is unlikely to happen; I mean nature may not intend it to be that way, or it may simply be because we have not used the correct doses. The dose of isoprenaline we use is the dose reported by others who have done exactly the same sort of experiments—about 40 μg/kg/hour. The reason that we do not exceed this dose is because experimental animals die if we do, and we do not give a lower dose than this because down-regulation is not achieved very quickly, so this is a very contrived model. In my view, attempting to draw an analogy to the human situation is impossible, but short-term interaction and short-term down-regulation experiments are more likely to represent the real situation in the early stages of heart failure than is removing an almost dead heart and estimating the receptor populations.

Dr. Parmley: Can I comment on that? I think in some ways it is a very predictable response. To block an agonist effect with an antagonist usually requires an excess of several 100-fold to a 1,000-fold of the antagonist. The reason for this is that the β-receptor systems, like all receptor systems, are geared to amplification systems. Whether you down-regulate or desensitize is determined by receptor occupancy and the relative on and off rate of the agonist and antagonist. An antagonist occupying the receptor only produces its effect while the receptor is occupied. When an agonist comes into contact with the receptor it induces a cascade effect activating multiple G proteins which in turn switches on the catalytic unit to produce multiple units of cyclic adenosine monophosphate (AMP). A very short treatment with an agonist results in a large effect, so you have to overwhelm the system with high concentrations of antagonists to block this.

Dr. Barnett: From the point of view of receptor occupancy, the concentration of isoprenaline in the rat heart at the end of the infusion period is equivalent to about a 10% receptor occupancy. We are therefore way down on the dose-response curve for isoprenaline from the point of view of functional effect, and yet we are able to produce maximum down-regulation indicating that a high isoprenaline concentration is not required.

Dr. Hori (Japan): Recently it has been claimed that antibodies to the β-receptor increase in the circulating blood, which may be the cause of heart failure. Are you able to comment on this?

Dr. Stiles: I do not know whether this is the case. It has been said for almost the last 15 years now that in a variety of conditions, including asthma and congestive heart failure, autoantibodies to the β receptor could explain the symptoms and signs. None of those studies have ever been corroborated by other laboratories.

Dr. Kupper: This question should be easily answered in the next 1 or 2 years when the receptor has been crystallized.

Dr. Parmley: May I ask a philosophical question of our 3 panelists? If you look at data in the literature regarding up- and down-regulation of receptors, you find people who argue it both ways in terms of congestive heart failure, that is, that with an increased concentration of catecholamines and down-regulation, the consequences are beneficial, preventing the deleterious effects of catecholamines on the heart. On the other hand if, for example, β blockers are administered and some up-regulation is allowed for, it is beneficial because a restored responsiveness to the system is achieved. So the philosophical question I am posing is whether this is good or bad and what is the best therapy?

Dr. Kupper: I clearly would make a statement in favor of β blockers as the therapy because it is clear that catecholamines given acutely or in excess harm the myocardium, but if you have no β receptors left then the heart probably cannot work sufficiently. This is why interrupting the pathophysiologic sequence that probably develops in congestive heart failure is the right way to treat this condition and in my opinion points to the use of blockers which restore β receptors.

Dr. Barnett: The β-blocker story is a little bit confusing, that is to say that if you administer β blockers to treat the patient with heart failure you titrate the dose and the patient recovers. However, the patient recovers even though the β blocker is still present, so the new receptors are actually blocked by the drug. I have never quite understood, therefore, how you could use that as a piece of evidence to indicate that up-regulation or reversing the problem was of benefit. You could argue that β blockade is simply preventing excessive stimulation of the heart and an excessive compensatory mechanism.

There is some very interesting work from Paris looking at messenger ribonucleic acid expression in hypertrophied hearts. It has shown that, for example, the calcium adenosine triphosphatase messenger ribonucleic acid is expressed during hypertrophy before the gene product, and research is now being conducted to see whether gene products associated with β receptors appear during hypertrophy, and whether the β receptor adaptation is truly part of the physiologic process. We need to find out what the first mechanism is, what actually happens at the beginning and I think once we can answer this question we will know better whether it is good or bad to have the receptors down-regulated or not and I don't think there is an answer to this at the moment.

Dr. Stiles: We all concentrate on total cyclic AMP production, yet we know that only so much cyclic AMP is needed to produce a full physiologic effect, and everything above that is surplus.

Dr. Camerini (Italy): We observed a subgroup of patients with reduced ejection fraction, poor exercise tolerance and histologic signs of active myocarditis. These patients had a persistent sinus tachycardia and an increased heart rate up to 170 or 180 when undergoing slight exercise, 20 to 40 W. The treatment with β blockers in these patients determined a definite significant reduction of heart rate and improvement of ejection fraction and of clinical signs. My question is: Is it possible to speak in some cases of up-regulation of β receptors and to have a beneficial result with β blockers in these cases?

Dr. Barnett: You could say that the excessive tachycardia in those patients was metabolically wasteful, and therefore by blocking it you were allowing a more appropriate use of the energy that they needed. I think that would be the way that I would explain it. The reason that we can treat some of those patients with β blockers is because we don't administer a high dose immediately, but gradually titrate upward until the required dose is achieved; doing this achieves a reduction in metabolic requirements.

Dr. Camerini: These patients were all at rest and following slight exercise had an abnormal response with tachycardia.

Dr. Barnett: Yes, I can give you an anecdotal case. I recently had a patient under my care who had very severe heart failure. She had severe ventricular tachycardia which was only controllable with amiodarone; she was on angiotensin-converting enzyme inhibitors and large doses of diuretics, and was in and out of hospitals on a regular basis. After getting her over acute episodes of pulmonary edema and informing her that she could return home the following day, she would become so excited that she would go into left ventricular failure that night, and we had to treat her again. We gave her a small dose of xamoterol and she improved dramatically, and I think that was simply because xamoterol was actually blocking the excessive sympathetic response in her heart which was just tipping her over the edge. I think a β blocker would have probably done just as well under the circumstances.

Dr Camerini's question raises a completely new issue; he refers to acute infectious disease of the myocardium in patients who have probably been treated with prednisone and immunosuppresive regimens in addition to the basic treatment, whereas in this workshop we have been considering patients in a relatively stable condition of chronic congestive heart failure.

Dr. McInnes (United Kingdom): As a confused clinical pharmacologist, I am impressed by the amount of catecholamines that seem to be around and also about the beneficial effects of β blockade in some circumstances, and I wonder what possible value the small amount of agonist in a drug like xamoterol can possibly be. Surely it is completely swamped by the catecholamines that are present and that all you are seeing with xamoterol is the effect of β blockade, as Professor Barnett has pointed out. I wonder if the panelists would like to discuss this.

Dr. Barnett: I believe that patients with severe heart failure who respond to β blockers are being protected from the excessive metabolic demands of the sympathetic nervous system, and these patients have already had everything in the way of conventional treatment, and they have tremendous compensatory mechanisms in operation. Xamoterol is available now for use in much lower grades of heart failure. I think they are 2 different groups. The anecdote I gave was, I think, in relation to the excessive sympathetic demands which could tip the balance in some severe heart failure patients and is quite separate. We just happened to use xamoterol because it seemed a safe β blocker in those circumstances. I would not say that was the way in which it principally works in the mild disease, but that is a personal view.

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Genesis of Arrhythmias in the Failing Heart and Therapeutic Implications

Celia Oakley, MD

Between 50 and 70% of patients with heart failure die suddenly and unexpectedly before they have deteriorated to New York Heart Association class IV symptoms. It has long been known that ventricular ectopy predicts sudden cardiac death in coronary heart disease, and this has also been shown in dilated cardiomyopathy. It is less certain whether antiarrhythmic drugs reduce this risk and improve prognosis. Supraventricular arrhythmias frequently develop in heart failure of all causes. They nearly always cause symptoms, and the establishment of atrial fibrillation may mark a permanent deterioration. Except for sustained ventricular tachycardia, ventricular arrhythmias are often occult. Hypokalemia and digitalis toxicity may have been precipitated by diuretics or interaction with antiarrhythmic drugs. In coronary heart failure, arrhythmias may be related to scar tissue or ischemia, which may also be responsible in dilated cardiomyopathy. Use of inotropes and inodilators may precipitate arrhythmias, whereas drugs that conserve energy or potassium, such as β blockers and angiotensin-converting enzyme inhibitors, may prevent them. Since suppression of ventricular arrhythmias has not been shown to prevent sudden death or prolong life in patients with heart failure, it may be that such arrhythmias do not directly presage ventricular fibrillation except in so far as they are markers of a poor prognosis with a risk of sudden death. If so, such arrhythmias are most likely to be suppressed by agents that result in improvement of left ventricular function and, through that, prolongation of life.

(Am J Cardiol 1991;67:26C–28C)

Arrhythmias are common occurrences in patients with heart failure. Supraventricular arrhythmias almost always cause symptoms and may mark a permanent deterioration in exercise performance. The onset of atrial fibrillation is almost invariable at some stage in rheumatic heart disease, and although left atrial pressure and size have an influence on its timing, many patients progress into irreversible chronic atrial fibrillation, even up to several years after successful valve replacement when left atrial pressure is close to normal. In most other forms of heart disease, atrial fibrillation, or (less often and more uncomfortably) chronic atrial flutter, develops in association with the onset of heart failure. Atrial flutter occurs more often in right-sided cardiac disease, particularly when it is not of rheumatic origin, whereas atrial fibrillation is more frequently seen in rheumatic, valvular, coronary or cardiomyopathic failure.

Ventricular arrhythmias may be precipitated by diuretic-induced hypokalemia or digitalis toxicity, often induced by interaction with antiarrhythmic drugs and hypokalemia. In coronary heart failure ventricular ectopy may be related to ischemia, and this may be exacerbated by treatment with inotropes or inodilators (Table I).

Except for sustained ventricular tachycardia, ventricular arrhythmias are often occult. Ventricular ectopic activity, uncommon in childhood, occurs more frequently with increasing age, especially in the elderly, even in the absence of heart disease. Ventricular ectopic activity has been shown to have adverse prognostic significance in coronary heart disease, and in dilated and hypertrophic cardiomyopathy. Sudden death is common in patients with heart failure. About 50% of patients with dilated cardiomyopathy die suddenly without a preceding period of hemodynamic deterioration, and this is presumably due to ventricular fibrillation. Such patients usually show considerable ventricular ectopic activity on ambulant electrocardiographic monitoring, and it has been assumed, but not shown, that suppression of this activity may reduce the chance of ventricular fibrillation, but death may result from sudden mechanical deterioration induced by the arrhythmia rather than from the arrhythmia itself. About 50% of patients with coronary artery disease also die suddenly even without heart failure. They also show ventricular ectopic activity, which has been shown to be an adverse prognostic indicator, but suppression of these arrhythmias has not been shown to prolong life. In patients with heart failure of coronary origin the risk of sudden death was shown to be over 70% in the study from Framingham. This explains why patients with cardiomyopathies comprise more than half of all patients who have undergone cardiac transplantation in most cen-

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TABLE I Possible Contributory Causes of Ventricular Arrhythmia In Heart Failure

Drugs	
Digitalis	(excess, interaction with antiarrhythmics, hypokalemia)
Diuretics	(hypokalemia)
Vasodilators	(hypotension and ischemia)
Inotropes and inodilators	(arrhythmogenic and proischemic effect)
Antiarrhythmic drugs	(proarrhythmic effect)
Electrolyte Imbalance	
K+	(diuretics and interaction with digitalis)
Mg^{2+}	
Neurohumoral Activation	
Sympathetic Renin-angiotensin	(arrhythmogenic)
Structural	
Ventricular hypertrophy Scar and aneurysm Dilatation	

ters, even though coronary disease is a far more common cause of death in the same age group. A small proportion of patients with coronary artery disease survive to go into heart failure or achieve a place on a transplant waiting list, and even fewer live to undergo transplantation because their prognoses are, individually, so unpredictable.

It has been assumed that suppression of ventricular ectopy with antiarrhythmic drugs leads to an improvement in prognosis, but this has not occurred in patients with either coronary heart failure or dilated cardiomyopathy. In a recent study the use of an antiarrhythmic drug was shown to increase mortality. In this study, performed in patients who had had infarction, the use of flecainide was associated with increased mortality and led to the recommendation that this drug should only be administered for the treatment of life-threatening arrhythmias. The use of amiodarone in dilated cardiomyopathy suppresses ventricular ectopic activity, but an increase in survival rate in patients treated with amiodarone has not been demonstrated. It is possible that the dose of amiodarone selected was too low and that the patients included in the trial were too sick (New York Heart Association classes III and IV) for benefit to be demonstrated, but this awaits further elucidation.

Again, these arrhythmias may reflect the severity of the underlying heart disease, and improvement of left ventricular function could lead to an improved prognosis. This could be achieved by agents that conserve potassium, such as angiotensin-converting enzyme inhibitors, or by conserving myocardial energy, e.g., with β blockers. A small-scale trial has found that captopril reduced ventricular ectopies and prolonged life while enalapril has been found to prolong life but not reduce the number of sudden deaths.

A study from the Hammersmith Hospital has examined survival from sudden death in patients with heart failure, and related this to the incidence of ventricular arrhythmias (Fig. 1). Survival was related to the severity of the disease; there were no deaths among patients with class I disease, and there was a progressively higher mortality among patients in classes II to III. However, there was little difference in survival between patients with ventricular tachycardia or more than 250 ectopies and those with no arrhythmias. In all patients, sudden death occurred more frequently as the mechanical function of the heart deteriorated.

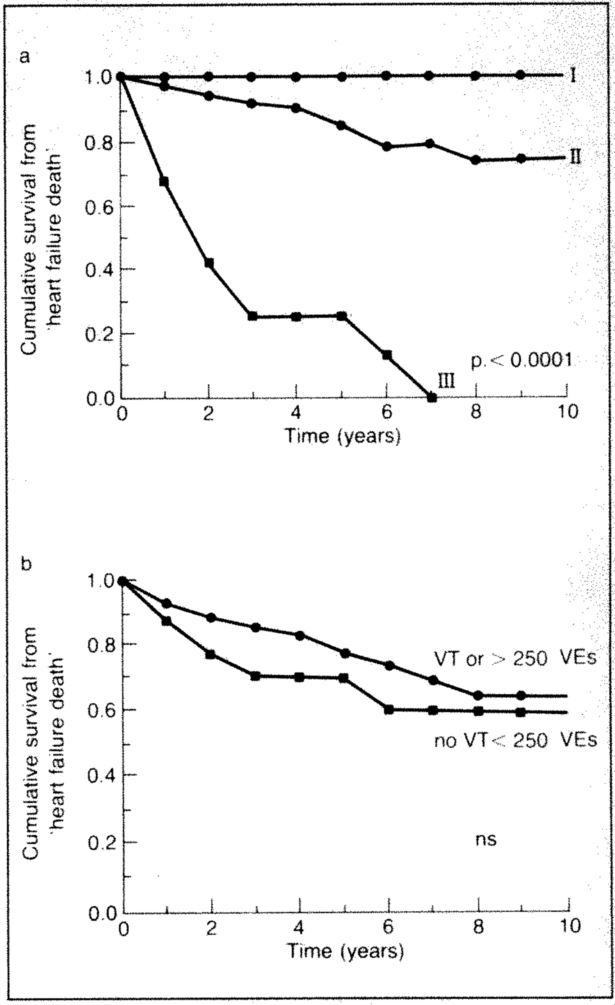

FIGURE 1. Cumulative survival in patients with heart failure. *Top*, survival in patients with New York Heart Association class I, II or III disease. *Bottom*, survival in patients with (presence of ventricular tachycardias, or more than 250 ventricular ectopies) and without arrhythmias. VEs = ventricular ectopies; VT = ventricular tachycardia. (Reproduced with permission from *Quart J Med.*)

If sudden death results from loss of mechanical function and reduced coronary blood flow rather than from arrhythmia, per se, this would have profound therapeutic implications. The key to preventing sudden death may lie in improving circulatory function and coronary blood flow, possibly by using angiotensin-converting enzyme inhibitors or β blockers.

In hypertrophic cardiomyopathy, sudden death is well known even in the absence of heart failure. Suppression of nonsustained ventricular tachycardia with amiodarone initially seemed to reduce the incidence of sudden death, but this has proved disappointing in long-term follow-up. Moreover, children with hypertrophic cardiomyopathy, although at greatest risk of sudden death, have the lowest incidence of arrhythmias. The use of antiarrhythmic drugs therefore seems to be inappropriate, because in children and in many adults the cause of sudden death may relate more to the hemodynamic vulnerability of the small, stiff, left ventricle than to primary arrhythmias. Secondary arrhythmias may be delayed in some cases but this has still to be established.

All forms of heart failure, and even the aging process itself, lead to myocyte loss and compensatory hypertrophy. Hypertrophy inevitably results in an increase in the capillary-myocyte distance and to an adverse change in the ratio between energy-producing mitochondria and energy-consuming myofibrils. The use of inotropes for the treatment of heart failure may increase this energy imbalance and enhance ischemia. Treatment designed to reduce energy expenditure by slowing the heart rate and reducing blood pressure and wall stress when this is possible may be more effective in reducing sudden death and prolonging life than the use of inotropes.

The long-term use of β-adrenergic blocking drugs may owe its beneficial effect in certain patients with heart failure to this energy-conserving effect.

The information that we have, incomplete though it is, leads us to conclude that ventricular ectopy seems to be a marker of severity in heart disease and thus of adverse prognosis. Reduction in arrhythmias with improvement in prognosis may come from the use of drugs that improve left ventricular function rather than from the administration of antiarrhythmic drugs, most of which have a negative inotropic effect as well as a proarrhythmic effect in some patients.

DISCUSSION

Dr. Parmley (San Francisco, California): What do you do when you have a patient with severe heart failure and you have done all you can about correcting all of the proarrhythmic factors that you have mentioned? We have no evidence that you can perhaps prolong life. Do you recommend an antiarrhythmic agent in these circumstances?

Dr. Oakley (London, United Kingdom): Yes, we use amiodarone because I think it may work. The fact that it was not shown to work in trials does not actually deter me if a patient is having ventricular ectopy, which I think is predictive of his death.

Dr. Barnett (Leicester, United Kingdom): What about the possibility that sudden death and arrhythmias are induced by small platelet deposition and the possibility of preventing arrhythmias by using antiplatelet drugs, "the aspirin story"?

Dr. Oakley: All our coronary patients take aspirin unless it is contraindicated. We don't usually give aspirin to patients with dilated cardiomyopathy, but there might be platelet aggregation in the microvasculature under certain circumstances.

Dr. Parmley: Certainly, in the setting of an unstable coronary syndrome, like unstable angina, aspirin has been a dramatic drug. It is interesting to note, though, that in a trial of stable coronary patients with silent ischemia, patients randomized to receive aspirin or placebo showed no decrease in silent ischemia (that is, there was no suggestion that there were platelet plugs or thrombi, or vasconstrictive substances released by platelets); so, you could make a strong case that aspirin would be useful in any unstable coronary syndrome where there is rupture of a plaque and platelets attaching to the vasculature, but apparently not in chronic coronary disease.

Dr. Wong Shou Pang (Hong Kong): What makes you feel that hypertrophic cardiomyopathy is more mechanical than arrhythmogenic, and would you be more liberal in recommending surgery in patients with hypertrophic cardiomyopathy if this is indeed the case?

Dr. Oakley: I am not an advocate of surgery for hypertrophic cardiomyopathy. Even the enthusiasts do not claim that there is any improvement in prognosis following surgery, or any reduction in sudden death; they admit an increase in the incidence of clinical heart failure after surgery.

Speaker: In view of the paper published some years ago, suggesting that survival time is correlated with the concentration of circulating catecholamines (particularly norepinephrine), would you advise the use of a drug like labetalol, blocking α and β receptors in small amounts.

Dr. Oakley: I would rather choose separate doses of α and β blockers and be selective than use a drug with both properties which was nonselective in respect of both the α and β blockade, so I would not use labetalol but an element of α and β blockade may well be what is needed.

Dr. McInnes (United Kingdom): In view of the fact that the vast majority of heart failure patients who are given diuretics do not become hypokalemic, how large a problem do you think hypokalemia is? Is diuretic-induced hypokalemia involved in the etiology of these arrhythmias?

Dr. Oakley: I think that in general practice, diuretic-induced hypokalemia may be quite a problem. I believe that there is a considerable amount of diuretic abuse, not just confined to out-of-hospital practice, but also in the hospital. When we admit patients with heart failure whose condition has deteriorated, it is very often necessary to reduce their diuretic intake. I think in that context hypokalemia may be common. I agree with good practice, which is using diuretics in low dosage and introducing an angiotensin-converting enzyme inhibitor early which retains potassium. For many years the administration of potassium supplements to patients in my unit has been totally forbidden. They are allowed to use potassium-sparing agents whenever necessary, but we do not ever use potassium supplements.

Adaptive Changes in the Periphery and Their Therapeutic Consequences

Helmut Drexler, MD, Thomas Münzel, MD, Urs Riede, MD, and Hanjörg Just, MD

Systemic vasoconstriction in chronic heart failure is due to several compensatory mechanisms with different time courses. Peripheral vasoconstriction mediated by increased sympathetic tone and activation of the plasma renin-angiotensin system may act primarily for short-term control. The effects of the vascular renin-angiotensin system, impaired flow-dependent, endothelium-mediated dilation (resulting from chronically reduced flow) and structural alterations of the vessel wall slowly emerge with time. In addition, fluid retention may contribute to increased vascular stiffness in chronic heart failure. Improved cardiac output with acute administration of vasodilators and inotropes is not immediately translated into increased blood flow to skeletal muscle, because (1) the reversal of the peripheral alterations described develops slowly over time (in fact, vasodilators and inotropes given acutely may cause redistribution of blood flow in skeletal muscle without improving oxygen availability); and (2) intrinsic abnormalities of skeletal muscle exist in chronic heart failure (e.g., due to chronic deconditioning, resulting in reduced oxidative capacity of skeletal muscle, as suggested by ultrastructural analysis and nuclear magnetic resonance spectroscopy). Drugs that interfere with the underlying compensatory mechanisms (e.g., renin-angiotensin system) without development of tolerance during long-term therapy exert beneficial effects after long-term treatment (e.g., the beneficial effects of angiotensin-converting enzyme inhibitors are, in part, due to peripheral mechanisms—the inability of the peripheral vessels to dilate—and to improvement of peripheral oxygen extraction).

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In recent years, it has become obvious that the degree of ventricular dysfunction in congestive heart failure (CHF) does not correlate with the severity of clinical CHF. Whereas left ventricular dysfunction represents a major independent predictor of prognosis, the functional status of patients with CHF (e.g., as assessed by exercise testing) appears to be unrelated to indexes of left ventricular dysfunction (e.g., ejection fraction). Franciosa et al[1] first reported this lack of correlation between exercise time and left ventricular ejection fraction, which has since been confirmed by several investigators.[2,3] However, although vasodilators or positive inotropes cause improvement in central hemodynamics, exercise duration and maximal oxygen consumption do not increase immediately after administration of these drugs. Thus, improvement in central hemodynamics is not immediately translated into enhanced exercise capacity in patients with heart failure. Whereas drug therapy does not reverse a primary cardiac insult (e.g., development of left ventricular scar) it may modify the compensatory mechanisms that cause progression of cardiac failure, worsening of clinical symptoms and reduced exercise tolerance. Cardiac mechanisms such as ventricular dilation and hypertrophy (including remodeling after infarction) are aimed to preserve systolic and diastolic function, thus maintaining cardiac output. When cardiac output remains inadequate, circulatory mechanisms emerge.[4] Systemic vasoconstriction is the hallmark of this second response, and is mediated by different mechanisms.

VASCULAR ADAPTATION IN CHRONIC HEART FAILURE

Zelis et al[5] noted that in patients with chronic heart failure, the increase in blood flow to working muscle with exercise is attenuated for each given work load compared with that in normal persons. Oxygen consumption at each level of work was lower in patients with chronic heart failure and was accompanied by an early increase in plasma lactate concentration.[5] The reduced maximal blood flow to working muscle during exercise appears to be confined to oxidative working muscle, as suggested by the investigators' recent studies (Fig. 1).[6] In a rat model of chronic heart failure, blood flow to glycolytic muscle fibers was adequately increased with exercise. However, the ability to increase blood flow to oxidative working muscle was impaired in this model of chronic heart failure.[6] Thus, the percentage of total muscular blood flow directed toward glycolytic (fast twitch) muscle fibers is increased. This may indicate a redistribution of blood flow to working muscle during exercise to those muscle

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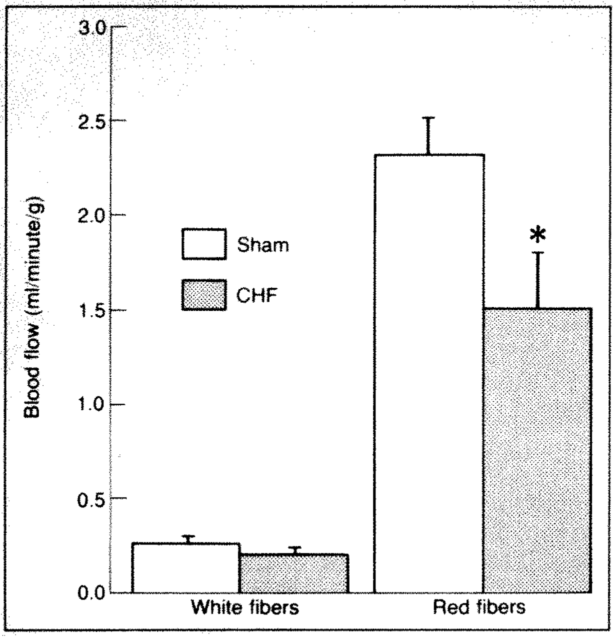

FIGURE 1. Redistribution of blood flow within skeletal muscle. *Open columns*, the sham-operated group; *hatched columns*, the heart failure group. The white fibers denote glycolytic muscle and the red fibers denote the oxidative fibers. *p <0.05 vs corresponding sham value. (Adapted from *Circulation*.[6])

fibers that are not heavily dependent on oxygen delivery in order to maintain force under anaerobic conditions.

A number of mechanisms are involved in the impaired metabolic vasodilatory capacity within skeletal muscle in patients with CHF. First, excessive sympathetically mediated vasoconstriction occurs in patients with CHF. Both neural and humoral mechanisms appear to be involved in this response, possibly with different time.[7] Recent studies by Davis et al[7,8] and Hasking et al[9] showed that increased spillover of norepinephrine and impaired norepinephrine clearance both contribute to elevated plasma norepinephrine concentration in CHF. It is likely that these mechanisms are primarily involved in the short-term control of vascular tone. Activation of the plasma renin-angiotensin system causes increased concentrations of angiotensin II, exerting strong peripheral and renal vasoconstriction. However, increased plasma concentration of vasopressin, and possibly endothelin, may contribute to increased systemic vasoconstriction in patients with more severe CHF.

Although these neural and neurohumoral factors can exert potent systemic and regional vasoconstriction, they do not completely explain the impaired vasodilating capacity within skeletal muscle in patients with chronic heart failure. The early work of Zelis et al,[5] and recently confirmed by Le Jemtel et al[10] (for large muscle mass in the exercising leg), indicates that this impaired metabolic vasodilation during exercise cannot be restored by α blockade with phentolamine. However, angiotensin-converting enzyme (ACE) inhibition does not restore impaired metabolic vasodilation after acute administration of phentolamine, indicating that blockade of the plasma renin-angiotensin system by ACE inhibitors does not interfere with blood flow to working muscle during exercise in patients with CHF.[11,12] Thus, mechanisms other than direct vasoconstrictor forces of norepinephrine or angiotensin II must be involved in peripheral vasoconstriction. A vascular stiffness component has been proposed (e.g., owing to the increased vascular sodium content, which may, in part, explain the attenuated vascular responsiveness to metabolic stimuli).[13] A recent study indicates that approximately one-third of the reduced maximal vasodilator response during exercise in patients with CHF can be attributed to increased sodium and water content. After substantial diuretic therapy in decompensated CHF, enhanced metabolic vasodilation was noted.[14] However, experimental and initial clinical data suggest that other mechanisms, such as vascular structural alteration and chronic functional adaptations are important contributors to the impaired peripheral vasorelaxation in CHF.

Chronic vascular deconditioning may be one mechanism by which the vascular vasodilatory function is affected. Sinoway et al[15] demonstrated that peak vasodilator capacity is higher in the active arms of tennis players than in normal subjects, and that improved vasodilator capacity can be induced by a training program.[16] Conversely, a delayed reversal of impaired vasodilation in patients with chronic heart failure was observed after heart transplantation.[17] Experimental studies by Langille et al[18] showed that a chronic decrease of blood flow causes a reduction in arterial diameter. This decrease in vessel diameter was only observed when an intact endothelium was present. After endothelial denudation of the vessel, no change in vessel diameter was noted after chronic decreases in blood flow, suggesting that this effect is endothelium dependent. Recent experimental studies by Kaiser et al[19] demonstrated that endothelium-dependent relaxation is impaired in a canine model of chronic heart failure. Conversely, chronic increase in blood flow is accompanied by an enhanced capability of the blood vessel to dilate[20] due to an enhanced release of the endothelium-derived factor, believed to be nitric oxide. Finally, endothelin,[21] a recently discovered vasoconstrictor synthesized by the endothelium, responds to the physiologic factors such as shear stress.[22] Vascular gene expression of endothelin is reduced in states of high blood flow.[22]

Chronic deconditioning (accompanied by lower peripheral blood flow) may reduce endothelium-dependent vasodilatory capacity, eventually leading to a reduction in vessel diameter. Recent studies indicate that flow-dependent dilation occurs in humans both in peripheral and coronary arteries.[23,24] The degree of vasodilation after maximal increases in blood flow (+350%) averaged 50 to 60% of the maximal effect of high-dose nitroglycerin.[23] However, several experimental studies showed that this mechanism of vasodilation operates in resistance vessels as well.[25-27]

However, experimental data support the idea that neurohumoral vasoconstrictors such as angiotensin II, norepinephrine or endothelin may act, in addition to their

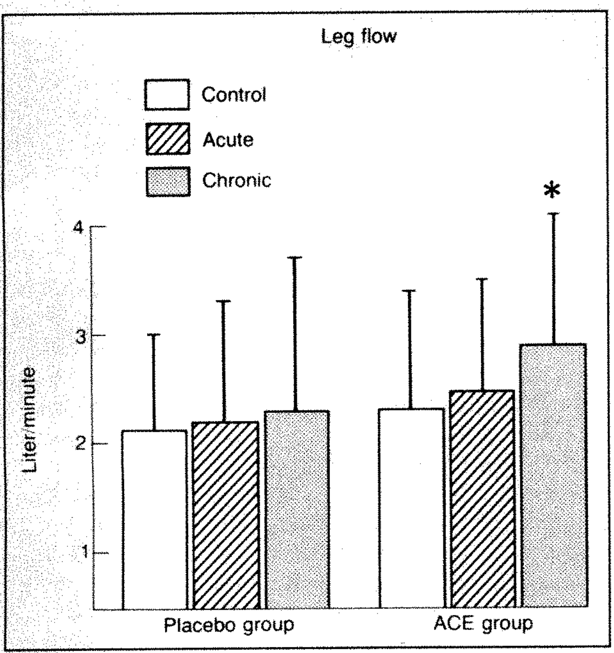

FIGURE 2. Femoral blood flow in patients treated with placebo or angiotensin-converting enzyme (ACE) inhibitors. Note that "acute" denotes measurements after short-term administration of the ACE inhibitor in both groups (later allocated to ACE therapy or placebo). *p <0.05 corresponding control value of the ACE group. (Adapted from *Circulation.*[10])

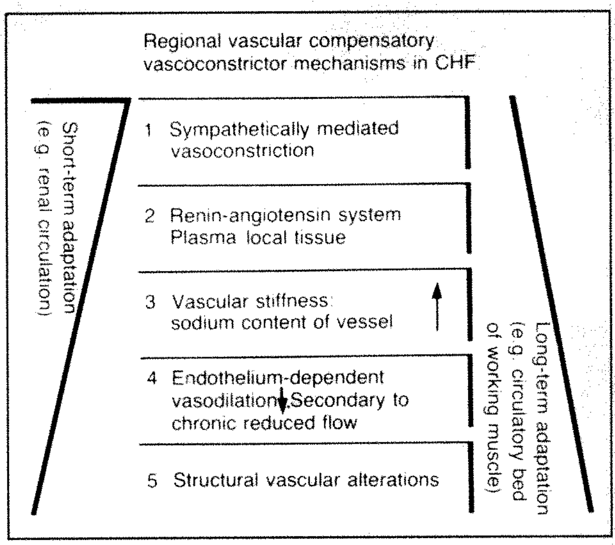
Regional vascular compensatory vascoconstrictor mechanisms in CHF
Short-term adaptation (e.g. renal circulation)
1 Sympathetically mediated vasoconstriction
2 Renin-angiotensin system Plasma local tissue
3 Vascular stiffness: sodium content of vessel
4 Endothelium-dependent vasodilation Secondary to chronic reduced flow
5 Structural vascular alterations
Long-term adaptation (e.g. circulatory bed of working muscle)

FIGURE 3. Possible mechanisms involved in the regional vascular responses in patients with chronic heart failure. CHF = congestive heart failure.

direct vasoconstrictor effect, as growth factors which, in turn, may cause structural vascular changes of the vascular wall. Experimental evidence indicates that angiotensin II induces hypertrophy of cultured rat aortic smooth muscle cells.[28] Angiotensin II and possibly endothelin and norepinephrine appear to be involved in the activation of proto-oncogenes. Evidence exists to indicate that the mas-oncogene encodes for an angiotensin-like receptor,[29] suggesting again that angiotensin is involved in the proliferative process of tissues during growth ("endogenous growth factor"). Recent observations indicate that ACE inhibition can reverse structural vascular alteration in a rat model of hypertension[30] and these beneficial vascular effects appear to be more prominent with ACE inhibitors than other antihypertensive drugs.[31] We recently observed that acute ACE inhibition does not alter femoral blood flow during exercise in patients with CHF. However, after chronic ACE treatment over 3 months, a significant increase in femoral blood flow was noted (Fig. 2).[12] Thus, chronic ACE inhibitor therapy reversed the inability of peripheral vessels to dilate. It is tempting to speculate that this effect was due to interference with the vascular tissue renin-angiotensin system, thereby reversing chronic structural alteration of the vessel. In fact, this mechanism of action would be consistent with the observation of the delayed beneficial effect of ACE inhibitor therapy.[32] Whereas the reversal of vascular alterations within working muscle may be emerging slowly over time, ACE inhibition does improve renal blood flow (and reduces renal vasoconstriction) dramatically after short-term administration of the ACE inhibitor. For example, captopril increased renal blood flow by 60% in patients with severe cardiac failure.[33] Obviously, different mechanisms (with different time courses) control different vascular beds. The renal circulation may depend more on mechanisms that can adapt immediately to intervention (e.g., with ACE inhibitors), in contrast to the vascular bed of skeletal muscle. The different vascular mechanisms proposed are seen in Figure 3.

INTRINSIC ALTERATIONS OF SKELETAL MUSCLE IN CHRONIC HEART FAILURE

As mentioned, there might be a shift from oxidative skeletal muscle to activation of more glycolytic working muscle fibers. This may indicate a change in the properties of the skeletal muscle itself. Interestingly, oxygen uptake of skeletal muscle during exercise cannot be improved in patients with chronic heart failure even when oxygen delivery is enhanced. Wilson et al[34] reported increases in blood flow to the exercising leg after administration of hydralazine as measured by thermodilution in the femoral vein.[34] However, it can be argued that this method determined blood flow in exercising skeletal muscle and inactive tissues. Other researchers did not observe an improvement in maximal blood flow to skeletal muscle during exercise.[10] To investigate this issue further, Drexler et al[6] determined blood flow to working muscle during exercise in the rat model of myocardial infarction and failure. Using the microspheres technique, this research team determined the blood flow to different muscles directly. Although milrinone increased peak blood flow to working muscle during exercise, peak oxygen consumption was not altered.[6] Thus, despite improved oxygen availability, oxygen uptake was unchanged. This observation suggests shunting of blood flow away from active muscle or intrinsic alterations of skeletal muscle in chronic heart failure, or both. Studies using different experimental methods to measure blood flow have subtantiated the latter hypothesis. Histologic examination of skeletal muscle revealed atrophy and increased intersti-

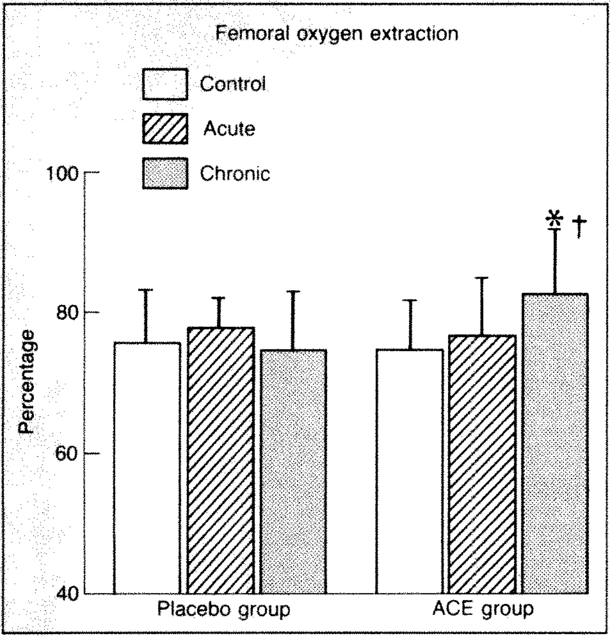

FIGURE 4. Femoral oxygen extraction in patients given placebo or angiotensin-converting enzyme (ACE) inhibitors. "Acute" indicates that the ACE inhibitor was given acutely in both the placebo and ACE group. *p <0.05 vs the corresponding control value of the ACE group. †p <0.01 for long-term treatment effects of placebo vs ACE inhibitor (Adapted from *Circulation*.[10])

tial cellularity as well as biochemical alterations of the skeletal muscle.[35] Ultrastructural analysis of skeletal muscle biopsy specimens has shown a reduced oxidative capacity of the muscle as indicated by a reduced volume density and reduced surface area of the cristae of mitochondria. In fact, a close relation has been found between the oxidative capacity of working muscle and the peak oxygen consumption during exercise.[36] Thus, the functional capacity (also known as the exercise capacity) may be, in part, determined by the condition of the working muscle. Previous studies have documented that the relation of maximal oxygen consumption and oxidative capacity of working muscle holds true, when investigating the oxidative capacity of skeletal muscle of sedentary and exercise-trained persons.[37,38] Recent experimental studies indicate that the muscles' aerobic capactiy is proportional to maximal oxygen consumption.[39] Similarly, biochemical analysis confirmed the investigators' ultrastructural data; i.e., enzymes involved in aerobic metabolism (e.g., succinate dehydrogenase or citrate synthetase) were reduced in patients with chronic heart failure.[40,41] The pattern obtained by nuclear magnetic resonance spectroscopy is consistent with these ultrastructural and biochemical observations.[42] The intracellular pH values during exercise are much lower for a given work load in patients with severe heart failure. Moreover, during exercise, the concentrations of plasma inorganic phosphate and phosphocreatinine decreased much faster in patients with heart failure than in normal persons.[42,43] Subsequent studies have excluded the possibility that these changes can be explained by different rates of blood flow to working muscle during exercise.[44–46] Although the mechanism for these alterations in skeletal muscle in patients with chronic heart failure is unknown, several potential mechanisms may be involved. Besides metabolic and nutritional influences, such as alcohol intake,[47] histologic and ultrastructural alterations in cardiac and skeletal muscle may be present in patients with idiopathic dilative cardiomyopathy as reported recently.[48] However, alterations in skeletal muscle have been found in patients with coronary artery disease (without peripheral vascular disease), which cannot be explained by a common systemic cause or disorder. Experimental and clinical studies have demonstrated that deconditioning, (e.g., stopping intense training in athletes) results in a substantial decrease in the concentration of oxidative enzymes within skeletal muscle.[49,50] Hence these intrinsic alterations may be due, in part, to chronic deconditioning of working muscle similar to the regression seen in athletes on stopping training. Studies to prove or exclude this possiblity are being conducted. Other contributory factors may be involved in these alterations of skeletal muscle, such as reduced blood flow (at least intermittently) or activation of the sympathetic action of the renin-angiotensin system, or both. In terms of reduced blood flow as a contributing mechanism, the energy status of cardiac muscle is closely coupled to myocardial blood flow.[51] Repeated episodes of reduced blood flow within skeletal muscle (e.g., to oxidative skeletal muscle only) may be involved in the hypothesized deconditioning process of skeletal muscle. Regardless of the potential underlying mechanisms previously discussed, there is evidence that these peripheral alterations of skeletal muscle are reversible. An intensive exercise training program, as well as treatment with ACE inhibitors, increases femoral oxygen extraction after long-term therapy (Fig. 4). It is tempting to speculate that these interventions improve oxidative capacity of working muscle. Combined improvement in femoral blood flow and in physical activity could account for this increased peripheral oxygen extraction.[12]

CLINICAL IMPLICATIONS

The marked improvement in cardiac output and filling pressures observed after treatment of patients with inotropic and vasodilating agents has prompted optimistic expectations that these improvements can be translated into beneficial long-term effects. However, most vasodilators or positive inotropic agents investigated failed to demonstrate such a sustained beneficial effect, even though some of these agents exert marked hemodynamic effects. Conversely, drugs that interfere with the underlying compensatory mechanisms in chronic heart failure (without development of tolerance) exert beneficial long-term effects as seen, e.g., with ACE inhibitors. These are, in part, related to their ability to reverse some of the peripheral abnormalities in patients with heart failure. It is also of interest that other vasodilator drugs that are likely to elicit beneficial long-term effects in chronic heart failure, act both as venous and arterial vasodilators (e.g., nitrates or, potentially, flosequinan). Finally, prolonged immobilization of patients with severe chronic heart failure has been advocated and this strategy is still widespread; in fact, restriction of physical activity is still recommended as a first step in treating patients with CHF.[52] However, patients with chronic heart failure often adapt their life style to a level of physical activity that is not associated with symptoms of heart failure. Further "prescription" of limited exercise may be disadvantageous with regard to peripheral adaptations. If the hypothesis previously outlined can be confirmed, the strategy of restricting physical activity may be questioned. This may be particularly true, if an effective therapy (e.g., ACE inhibitors) is initially instituted. Controlled physical activity may prevent peripheral deconditioning. However, until such an approach can be recommended, much basic and clinical research has to be done, and not all patients with heart failure can undergo intensive exercise both for safety and practical reasons.

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DISCUSSION

Dr. Hori (Japan): A recent study demonstrated that angiotensin II induced growth of vascular smooth muscle cells. If your hypothesis is correct, then angiotensin induces chronic hypertrophy and enhances vascular constriction. Do you have any idea as to whether endothelium-derived relaxing factor blocks hypertrophy or vascular smooth muscle?

Dr. Drexler (Freiburg, Federal Republic of Germany): There are no data available so far. I agree that angiotensin is obviously a growth factor and probably a very important one in the vascular wall. Langille et al[1] have shown that denudation of the vessel results in structural changes in the vascular wall. In my view this indicates that the endothelium is important in mediating changes in the vessel wall. Whether the changes are endothelium dependent in terms of endothelium-derived relaxing factor is a matter for debate. A recent report suggests that nitric oxide-generating vasodilators inhibit mitogenesis and proliferation of cultured rat vascular smooth muscle cells.[2]

Dr. Parmley (San Francisco, California): How would you interpret data concerning intermittent dobutamine treatment where it appears that patients receiving the drug seem to have an immediate increase in exercise tolerance which is sustained over a period of time after 2 to 3 days of infusion.

Dr. Drexler: In patients receiving dobutamine therapy, blood flow cannot be improved acutely. However, blood flow can be improved over a number of days. We have looked at β receptors in the skeletal muscle of patients with heart failure and could not find any down-regulation. It might be that the muscle is degenerating. Dobutamine has β_2-adrenergic activity, and changes in blood flow and cardiac output which may occur as a result of dobutamine infusion would be due to the fact that there is no down-regulation of the central receptors. Finally, I am not aware of a placebo-controlled study showing a definite beneficial effect of intermittent dobutamine.

Dr. Barnett (Leicester, United Kingdom): Has anybody conducted experiments on blood flow, and treated the reduced flow with nitrates, to try and replace the endothelium-derived relaxing factor? There is good evidence to show endothelium-derived relaxing factor response is desensitized if chronically treated with nitrates. Can you show that the treated tissue is less responsive to endothelium-derived relaxing factor-induced vasodilatation? In other words, is there some factor in chronic flow reduction that desensitizes the response to endothelium-derived relaxing factor resulting in a fixed constricted artery?

Dr. Drexler: We know that chronic flow reduction causes changes in the diameter of blood vessels, and that increased blood flow results in an increased release of endothelium-derived relaxing factor. It is also known that endothelium-dependent relaxation is reduced in chronic experimental heart failure. The underlying cause of heart failure is unknown, although the findings I have referred to suggest that reduced blood flow may be a contributing factor. Reduced blood flow results in a chronically decreased shear stress, which is believed to be a major stimulus for the release of endothelium-derived relaxing factor. To date, no studies have investigated the effect of therapy on endothelium-dependent mechanisms during heart failure.

Dr. Barnett: What you are saying is that if blood flow is reduced, endothelium-derived relaxing factor is required to counteract the reduced flow by maintaining the caliber of the vessel. There is presumably a balance between blood flow and other stimulatory factors, including endothelium-derived relaxing factor, which keeps the vessel dilated. If blood flow is reduced chronically and more endothelium-derived relaxing factor required to counteract this, either the response is desensitized or reduced quantities of endothelium-derived relaxing factor is produced.

Dr. Oakley (London, United Kingdom): I find it difficult to believe that the changes in skeletal muscle are not the combined result of reduction in blood flow and deconditioning, because if the patient cannot exercise he becomes increasingly unable to exercise; therefore, there is both a training effect and an effect which might arise if heart failure and the delivery of oxygen to the exercising muscles improved. It is not easy to measure blood flow to exercising muscle, and I think that most of the agents that improve the patient's condition may not improve the blood supply to exercising muscle very much. Certainly a patient can exercise more shortly after transplantation. I suspect that biochemical changes in the muscle are reversible, and certainly the changes to the mitochondria are very likely to be quickly reversible.

Dr. Drexler: In terms of the model with cardiac transplantation, an improved exercise capacity can be demonstrated very shortly after transplantation, but if these patients are followed over time the exercise capacity continues to improve dramatically. Thus, exercise capacity is not changed acutely. I try to convince people that a great deal can be attributed to training.

Dr. Oakley: I think all this interest in skeletal muscle is fine, but changes in skeletal muscle are a consequence of the poor blood supply and deconditioning. If central hemodynamics are changed for the better, then the patients will be able to exercise more, partly immediately, and then further as a result of the effects of training. That is obvious even without all this research.

Dr. Drexler: I do not think it was obvious to many people for a long time.

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Assessment of Exercise Tolerance in Chronic Congestive Heart Failure

Alain Cohen Solal, MD, and René Gourgon, MD

In patients with chronic heart failure, exercise capacity is poorly related to cardiac hemodynamics, and peripheral circulation is an important determinant of exercise tolerance. The ability of the muscle vasculature to dilate is markedly impaired, in part, because of exaggerated neurohumoral activity increasing vascular wall stiffness. For this reason, increasing cardiac output is not sufficient to increase exercise capacity if not accompanied by improving vascular reactivity. The poor reliability and reproducibility of exercise tolerance assessed by maximal exercise duration or maximal attained work load (particularly on a treadmill) has led to widespread measurement of respiratory gas during exercise. Peak oxygen consumption (peak $\dot{V}O_2$), even if it is symptom-limited, has been shown to be a very reproducible criterion of exercise tolerance; moreover, because $\dot{V}O_2$ is the product of cardiac output and arteriovenous oxygen difference, it also has a qualitative hemodynamic significance. Ventilatory threshold can be determined before maximal exercise; however, problems of determination limit the practical value of this criterion. Unfortunately, peak $\dot{V}O_2$ lacks sensitivity to detect minor improvement or impairment of symptoms during daily life, although these are significant to the patient. Submaximal exercises have been proposed for this purpose and are currently being evaluated.

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Exercise testing is often used in cardiology to quantify myocardial ischemia, but its realization in chronic congestive heart failure (CHF) has long been limited to therapeutic trials.[1] The rationale for widespread use of exercise tests in these patients is based on the poor relation between central hemodynamics and exercise tolerance, and the limitations of assessing functional state using the New York Heart Association (NYHA) criteria. However, the reliability and reproducibility of the usual criteria of exercise tolerance (maximal duration, maximal work load) not being perfect, physicians have looked for new methods to assess exercise tolerance objectively, namely, by respiratory gas analysis.[2–4]

REASONS FOR PERFORMING EXERCISE TESTS IN CONGESTIVE HEART FAILURE

The reasons for performing exercise tests in CHF are twofold: (1) the relation between central hemodynamics and exercise tolerance is poor, and (2) the NYHA classification lacks sensitivity. The poor correlation between exercise tolerance and central hemodynamics results from the general observation that functional impairment and reduced exercise tolerance are the direct consequences of circulatory dysfunction. If cardiac dysfunction is the main determinant of this circulatory failure, it is not the only determining factor; pulmonary, vascular and muscular abnormalities cannot be underestimated (Fig. 1). Symptoms of circulatory dysfunction during exercise consist of fatigue or dyspnea, or both. Dyspnea results from complex mechanisms, essentially an increase in capillary wedge pressure, in physiologic dead space, peripheral muscle underperfusion and perhaps respiratory muscle fatigue[5]; fatigue is the consequence of reduced muscle blood flow and abnormalities in muscle metabolism.[6] Several studies have consistently shown that resting ejection fraction, cardiac output or pulmonary wedge pressure correlate poorly with exercise tolerance.[3,7,8] Indexes of diastolic dysfunction of the left ventricle are a little better correlated with exercise duration.[9] These discrepancies can be explained first by the fact that the aforementioned criteria measured at rest do not always correlate with exercise criteria because of the existence of a cardiac reserve, and second because peripheral adaptation is underestimated. Various studies performed in the last few years have shown that exercise tolerance is at least as dependent on peripheral circulation as it is on cardiac function.[10–14]

The second reason for performing exercise tests is the subjective and nonparametric nature of the NYHA classification. There is clinical evidence that patients in NYHA class IV are well categorized by a questionnaire

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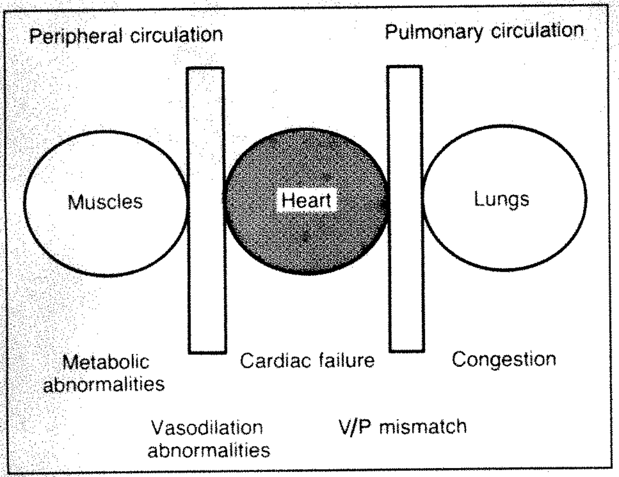

FIGURE 1. Limitation of oxygen transport during exercise in chronic heart failure. Cardiac failure leads to abnormalities in the whole system of oxygen transport. Pulmonary congestion decreases the compliance of the lungs, increasing the work of breathing and participating in the sensation of dyspnea. Ventilation-circulation mismatch may also limit oxygen transport. Abnormalities of the peripheral circulation are a major determinant of exercise tolerance. The inability of the peripheral vessels to dilate normally during exercise is the main factor responsible for reduced maximal muscle blood flow. Abnormalities of the metabolism of the muscle cell prevent optimal utilization of oxygen. V/P = ventilation/perfusion.

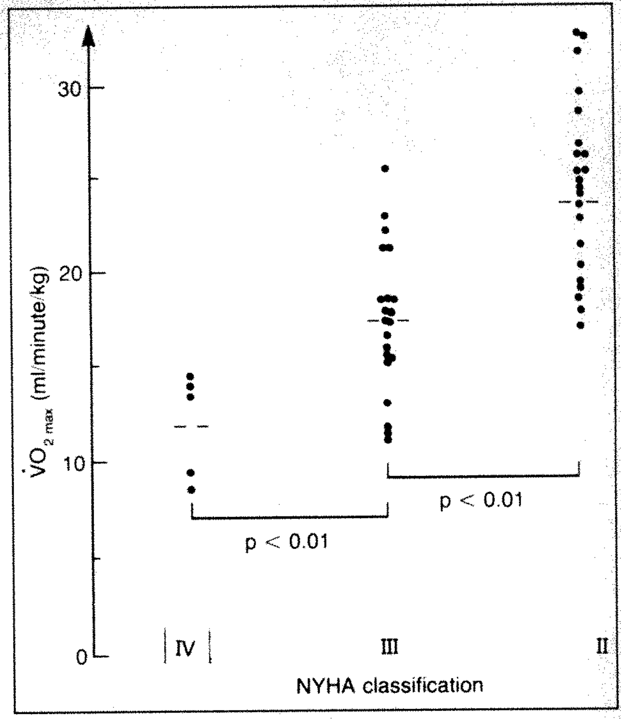

FIGURE 2. Limits of the New York Heart Association (NYHA) classification. The NYHA classification (x axis) is subjective, nonparametric and lacks sensitivity. If patients with the most severe congestive heart failure (class IV) are generally adequately categorized, there is a considerable overlap in maximal oxygen uptake ($\dot{V}O_2$max) between class II and III.

about their symptoms; for these patients, exercise testing only provides complementary information. However, discrimination between class II and III is more difficult (Fig. 2); most of the patients are in these categories and small but clinically important changes in functional status may not be detected. Interobserver variability in classifying patients within these classes is important. Therapeutics can modify this evaluation; how does one classify a previously asymptomatic patient in whom pulmonary edema develops? In recent years various questionnaires have been proposed in order to improve the assessment of the functional state, but they are still highly dependent on subjective considerations.[15,16]

RATIONALE FOR RESPIRATORY GAS ANALYSIS DURING EXERCISE IN PATIENTS WITH CONGESTIVE HEART FAILURE

The usual criteria for the determination of exercise tolerance have limitations; first, the protocol has a significant influence on the results of the test. Treadmill exercise mimics usual activities but is not widely used in continental Europe. The most important limitation of this technique is that it is difficult to rely on the predicted work. Nomograms are derived from data obtained in normal subjects; mechanical efficiency is dependent on body weight and work load can be affected by the subject holding on to the exercise rail, or by the way the subject moves on the treadmill. Bicycle ergometers also have disadvantages, as exercise is nearly always limited by fatigue of the quadriceps, and obese patients are at an advantage using this technique. However, when measuring oxygen uptake, this method yields fewer artifacts. It is accepted that each protocol should consist of long stages built up over a number of short increments. Patients with severe heart failure, however, have a very slow metabolic and hemodynamic response to exercise and sometimes never reach a steady-state at any stage. In normal subjects, exercising for longer than 15 minutes leads to boredom[17]; the same is probably true of patients with CHF. It appears that a ramp protocol with small increments (e.g, 10 W/min) was better tolerated and yielded fewer ventilatory or electrocardiographic artifacts than longer protocols. Finally, differences in the design of protocols make the comparison of results from different studies difficult.

The second limitation of conventional criteria for the determination of exercise tolerance is that exercise duration is dependent on the patient's motivation; the subjectivity of the physician may also influence the results. Work efficiency may vary from one patient to another and it is speculative to estimate oxygen uptake from work performed (Fig. 3). Finally, it is questionable to perform uncontrolled therapeutic trials in patients with CHF without respiratory gas analysis, particularly in those in NYHA class II. It is impossible, in the presence of a reduced exercise duration, to be sure that the reason for discontinuing exercise is circulatory failure and not poor motivation, deconditioning or respiratory insufficiency.

For all these reasons, respiratory gas analysis during exercise has been advocated in patients with CHF. Oxygen uptake ($\dot{V}O_2$) is the product of cardiac output by arteriovenous difference for oxygen; maximal oxygen up-

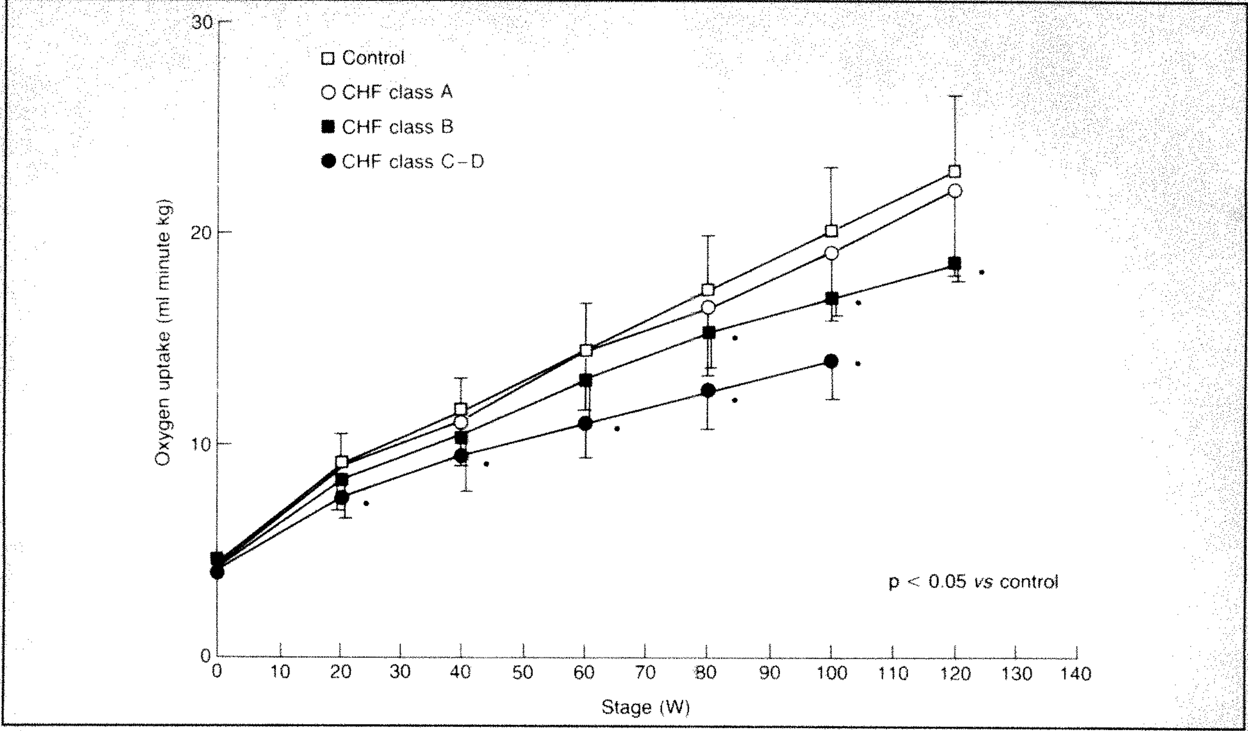

FIGURE 3. Oxygen uptake during bicycle exercise in patients with congestive heart failure (CHF). There is a wide range of $\dot{V}O_2$ values within each group which prevents any indirect estimation of $\dot{V}O_2$ without respiratory gas analysis. Patients in class A (peak $\dot{V}O_2$ <20 ml/min/kg) are not different from the control group (C) at identical work loads. However, $\dot{V}O_2$ becomes lower as the severity of congestive heart failure increases from A to C–D. (Personal data.)

take ($\dot{V}O_2$max) is the maximal value of $\dot{V}O_2$ reached by a normal subject. $\dot{V}O_2$max represents the maximal capacity of the body to transport oxygen to the tissues and to use this oxygen during exercise. $\dot{V}O_2$max has been defined as a plateau in the increase in $\dot{V}O_2$ at the end of the exercise. For this reason, $\dot{V}O_2$max is easy to determine and its reproducibility is impressive in normal trained subjects. As maximal arteriovenous difference for oxygen does not differ greatly between normal subjects, $\dot{V}O_2$max has been shown to be closely related to maximal cardiac output. Oxygen uptake, carbon dioxide production ($\dot{V}CO_2$), minute ventilation, breathing rate and other respiratory measures can now be easily measured on-line, by modern analyzers, without significantly increasing the duration of the test.

It was hoped that $\dot{V}O_2$max in patients with CHF as in normal subjects would be an objective and very reproducible criterion of exercise tolerance, independent of the patient's motivation. Unfortunately, patients with CHF rarely reach a true $\dot{V}O_2$max; so, the maximal value of $\dot{V}O_2$ obtained, called peak $\dot{V}O_2$, is symptom-limited and thus is not independent of the patient's motivation. It is now well known that in patients with CHF, peripheral circulation is the limiting factor of oxygen transport and peak $\dot{V}O_2$ appears to be related more to peak muscle blood flow than to maximal cardiac output. Nevertheless, we believe that peak $\dot{V}O_2$, although symptom dependent, is the most reproducible criterion of exercise tolerance in CHF (Fig. 4).[18,19] As such, it permits categorization of patients in a more objective and parametric way than is provided by the NYHA classification or the maximal exercise duration. Patterson et al,[20] and more recently Franciosa[2] and Weber et al,[3] proposed classifying the functional capacity of patients with CHF by their $\dot{V}O_2$max into 4 classes: (1) $\dot{V}O_2$max >20 ml/min/kg; (2) $\dot{V}O_2$max 16 to 20 ml/min/kg; (3)$\dot{V}O_2$max 10 to 16 ml/min/kg; and (4) $\dot{V}O_2$max <10 ml/min/kg. Other limitations come into play for the expression of peak $\dot{V}O_2$; indexation of $\dot{V}O_2$ by body weight alone is unsatisfactory; age, gender and fitness should be taken into account. Finally, one should determine if peak $\dot{V}O_2$ is really independent of exercise protocol (treadmill or bicycle, slow or rapid protocols).

To overcome these limitations, Wasserman et al[21] proposed an index of exercise capacity that seemed to be independent of the patient's motivation, making the index objective and reproducible, without necessitating achievement of a maximal exercise: the anaerobic threshold. The anaerobic threshold has been defined as the point at which plasma lactate concentration increases during incremental exercise. This lactate threshold is thought to result from a transition from aerobic to anaerobic metabolism in the peripheral muscle during exercise because of limitation of oxygen transport. The buffering of plasma lactate during exercise leads to an increase in CO_2 production, an increase in ventilatory drive and an increase in the respiratory exchange ratio (R = $\dot{V}CO_2$/$\dot{V}O_2$), making it simple, in normal subjects, to determine a ventilatory threshold closely related to the lactate threshold by respiratory gas analysis. However, considerable criticisms have been addressed to this concept; it is now widely accepted that a nonlinear increase in plasma lactate concentration or ventilation results from far more complex mechanisms than simply from a shift in metabolism.[22] Nevertheless, even if some controversies persist concerning the temporal relation between the lactate and the ventilatory thresholds, and the interobserver agreement in determination of the ventilatory threshold,[23] it is generally assumed that this noninvasive index is an important criterion of exercise tolerance in normal subjects.[24]

In patients with CHF, Weber et al[3] and other investigators[3,25,26] emphasized the value of the ventilatory threshold. Wilson et al[27] reported more pessimistic results. The first criticism against the use of ventilatory threshold in CHF is that, because of the ventilatory pattern of patients with CHF, a clear ventilatory threshold is sometimes difficult to detect; moreover, in patients with severe CHF or with marked deconditioning, a progressive increase in lactate and in $\dot{V}CO_2$ is observed from the beginning of exercise, invalidating the concept of an "anaerobic" threshold.[18] The $\dot{V}O_2$ French Study Group[19] has shown in a multicenter study that ventilatory threshold can be determined during exercise in up to 75% of patients with mild to moderate CHF; however, inability to determine ventilatory threshold in the remaining 25% of patients presents a serious limitation to widespread use of this criterion as a primary end point in therapeutic trials. Moreover, interobserver variability in the determination of ventilatory threshold cannot be ignored. Finally, reproducibility of ventilatory threshold measurements is inferior to that of peak $\dot{V}O_2$.[14]

Nevertheless, determination of the ventilatory threshold can potentially be used as an index of patient motivation; failure to reach the ventilatory threshold strongly suggests a poor motivation or a noncardiovascular limitation of exercise tolerance. Assessment of peak $\dot{V}O_2$ alone can be misleading; change in peak $\dot{V}O_2$ without change in the ventilatory threshold suggests an alteration in patient motivation rather than a change in functional capacity.

PERSPECTIVES

Computerized analysis of the $\dot{V}O_2/\dot{V}CO_2$ relation could improve the accuracy in the detection of the ventilatory threshold.[28] As peak $\dot{V}O_2$ is symptom-limited, Buller et al suggested extrapolation of $\dot{V}O_2$max from a computerized analysis of the $\dot{V}O_2/\dot{V}CO_2$ relation.[29] Finally, the slope of the oxygen uptake/time response curve during exercise has been proposed as a simple index of work efficiency: the greater the reduction in the slope, the higher the degree of anaerobic metabolism involved and the greater the severity of circulatory failure (Fig. 3).[29]

An important limitation of classic incremental exercise testing is that it does not really mimic the daily activities of the patients under observation. Obese women and patients with severe CHF are often poorly motivated or frightened by a maximal exercise test. Moreover, it is now clear that improvement in functional status and in peak $\dot{V}O_2$ does not always occur together. A decrease in pulmonary congestion or an increase in cardiac output during submaximal exercise allows a marked improvement of symptoms without an immediate increase in peak $\dot{V}O_2$; improvement of the peripheral circulation is a long-term process and is delayed compared with the improvement of cardiac function. For these reasons, submaximal tests have been proposed. Constant submaximal work load bicycle exercise tests have been studied by different groups.[30-32] However, the end point of these exercises remains to be defined[33]; for aerobic exercises, duration can be unlimited. In most other protocols, a regular increase in plasma lactate concentration is observed from the beginning of exercise and the test is rapidly stopped, suggesting that reduced muscle blood flow is the limiting factor. However, it is difficult to standardize these protocols. Finally, because respiratory gas analysis is still expensive and uncomfortable for some patients, the walk test should be considered[34]; it has been shown to be well tolerated in patients with CHF,[35] but more studies are required to assess the value of this method.

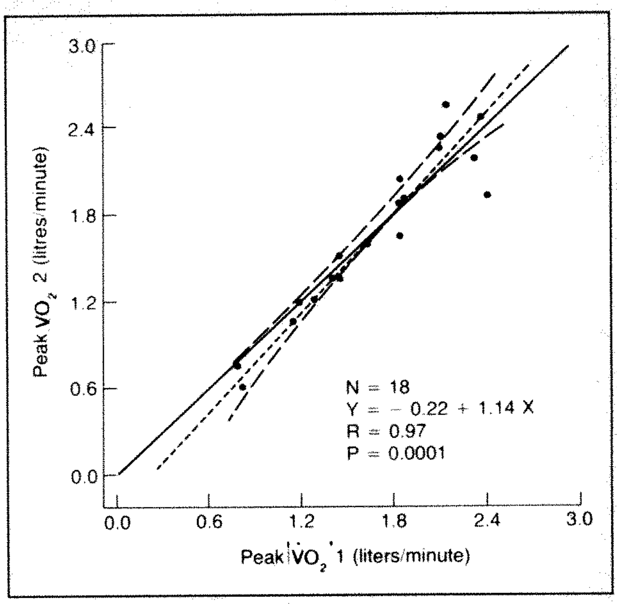

FIGURE 4. Reproducibility of peak oxygen uptake (peak $\dot{V}O_2$) during bicycle exercise in patients with CHF. Despite the fact that it is symptom-limited, peak $\dot{V}O_2$ is a highly reproducible criterion of maximal exercise tolerance.

CONCLUSION

Exercise testing is a useful tool for assessing the severity of CHF and the evaluation of therapeutics in CHF. Measurement of gas exchange permits greater understanding of the pathophysiology of the symptoms and provides a more objective method of assessing responses to pharmacologic interventions. However, exercise testing, even with respiratory gas analysis, is not the panacea,[36] and more studies are required to improve the criteria of evaluation of the functional state of patients with CHF.

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Assessment of Quality of Life

David B. Barnett, MD

Assessment of quality of life has emerged in recent years as an important part of the overall evaluation of drug therapy and health care in general. Measurement techniques for this difficult assessment range from simple unqualified questions on patient well-being to complex statistical analyses of a wide range of lifestyle and activity variables. The factors that influence quality of life during chronic drug therapy differ in the treatment of symptomatic (e.g., heart failure) vs asymptomatic (e.g., hypertension) disease, and include drug side effects, relief of symptoms, improved prognosis, return to work, physical activity and the need for further hospital treatments. The manifestation of quality of life varies for different people leading to lack of agreement on the precise definition. The absence of standardization of methods of measurement also contributes to this and leads to lack of comparability of studies and unreasonable claims by some drug manufacturers. Further complicating issues in multicenter trials across countries include language problems and interethnic differences in "sickness" behavior. The recently introduced quality-adjusted life year (QALY) index, designed to take account of both the quality and duration of life in assessing the outcome of treatments, may avoid some of these problems. By classifying illness states (the Rosser index) on the basis of disability and distress, and comparing outcomes in terms of improved prognosis, QALYs have already been used for cost/benefit analyses of a number of new and expensive therapies. Like other methods, QALYs have problems related to variability in individual appreciation of life values. To date, a perfect method of quality of life assessment remains elusive.

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A rapidly growing body of published reports on quality of life (QOL) assessment indicates the importance of this concept in the field of health care. In particular, QOL assessment has emerged in recent years as an almost essential part of the evaluation of new drugs from the point of view of their effects on both the patient and the economics of the community. The recent appreciation of the relevance of QOL measurements relates to the changing patterns of disease in Western society and to a shift in emphasis in the aims of treatment from concerns over acute and immediately life-threatening conditions to the management of chronic, slowly progressive, degenerative diseases.

DEFINITIONS

The degree of interest in QOL has not been matched by a commensurate level of expertise in its measurement. Methods of assessment range from simple unqualified questions on patient well-being to complex statistical analyses of a wide range of lifestyle and activity variables.

The difficulties that are experienced in measuring QOL stem from the lack of an adequate definition, as QOL manifests itself differently to different people at different times, and is different for various diseases. However, various terms that relate to QOL, some of which are objective and others that are dependent on variable subjective assessment, need to be defined:

Health—a hypothetical state without agreed definition dependent on social and economic factors.

Disease—labeling and diagnostic categorization based on objective pathologic clinical criteria.

Illness—subjective perception by a patient of unusual/unpleasant feeling that may lead to differential behavior patterns.

Sickness—behavioral patterns used to indicate the presence of illness (e.g. seeking medical help, going to bed to rest, staying away from work).

It follows from these definitions that there will be considerable variation in the assessemnt of the impact of disease on different subjects. Thus, a person can feel ill and manifest sickness behavior without having a disease in the true sense. Conversely, an individual may feel well while still harboring a disease process or stoically resist manifesting sickness behavior despite feeling very ill.

FACTORS INFLUENCING QUALITY OF LIFE

Symptoms and adverse effects: QOL assessment is highly dependent on the nature of the underlying disease process, in particular, whether it is symptomatic or asymptomatic (Table I). Thus, in an asymptomatic condition (e.g., hypertension) the impact of the side effects of the drugs used will have a significant influence on QOL.

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TABLE I Quality of Life Assessment

Condition	Risk	Benefit
Asymptomatic (e.g., hypertension)	Early death drug side effects, disability (e.g., stroke)	Improved prognosis, longer life, decreased risk of disability
Symptomatic (e.g., heart failure)	Early death, severe symptoms dyspnea, fatigue, drug side effects, loss of earnings, social problems	Improved prognosis, reduced symptoms Getting back to work, improved social life

Thus, the recent Medical Research Council trial in asymptomatic hypertension found no reduction in overall mortality and only a small benefit in terms of the number of strokes in the actively treated group.[1] An important discussion point to arise out of this trial has been the relation between the magnitude of this modest benefit and the cost of treatment, both in terms of economic costs to the National Health Service and in terms of drug side effects experienced by the patients.[2] Over the years of the Medical Research Council trial 16% of patients receiving active treatment withdrew because of adverse effects resulting from drugs used in the trial (bendrofluazide and propranolol) including gout, impotence, lethargy, nausea and headaches. In addition, an increased incidence of symptoms of depression has been noted in patients treated for mild hypertension and this has also been associated with an increased use of tricyclic antidepressant drugs.[3] This latter effect represents a significant impairment of QOL whether it is a direct consequence of treatment with tricyclic antidepressants due to the treatment of hypertension or related to psychologic factors associated with the patients' awareness of the diagnosis.

Conversely, when treating a symptomatic condition (e.g., heart failure or angina) the adverse effects of therapy (drugs or surgery) are set against the alleviation of distressing symptoms. The overall effect of treatment on QOL will therefore be appreciated by the patient as a balance between these 2 factors. Thus, patients with major cardiac disease often experience severe fatigue, which results in a significant reduction of everyday activities often leading to reduced emotional well-being and disruption of family relations. Successful treatment, either medical or surgical, will be readily appreciated by the patient as directly contributing to improved QOL.[4]

Patients' tolerance of drug side effects is dependent on many factors including an appreciation of potential long-term benefits (e.g., reduced likelihood of disability or early death). However, there are limits to this tolerance, and much to the surprise of many physicians, some patients prefer to take their chances on a potential future hazard rather than endure adverse reactions to drug therapy while they "feel well."

Gender/age and cultural background: A number of innate and environmental factors influence individual perception of disease and the manifestations of sickness behavior. These factors may be "biologic" but are more often psychologic, e.g, the "reduced" appreciation of pain in men that is often related to the male perception of being the "stronger" sex. Ethnic and cultural differences may be more complex. Thus, different cultural groups will vary considerably in their reporting of symptoms because previous experience of disease processes and expectations of health are very different between different countries.[5] These factors may complicate QOL assessment when close-knit ethnic groups form part of a clinical drug trial outside their normal environment (e.g., immigrant populations). Therefore, it is important that the methods of QOL assessment are applicable across different ethnic groups in order to avoid potential errors.

METHODS OF QUALITY OF LIFE ASSESSMENT

Most QOL assessment depends on the use of questionnaires, the design of which is obviously dependent on the aspect of QOL being investigated. Thus, in a disease-oriented approach, questions of medical relevance relating to symptoms or objective evidence of limited function will be used. If there is to be an emphasis on illness, then questions relating to fatigue, loss of interest in family, sexual difficulties or sleep disturbances are more relevant. Finally, concern over sickness behavior can be evaluted by raising questions such as how frequently the subject uses health services, takes medicines and takes time off from work.

The choice of which questionnaire to use is a vital one, for its content must be closely related to the nature of the medical condition being treated as well as to the effects of the drug or other treatment under assessment. Thus, a questionnaire suitable for assessment of the results of therapy for mild hypertension may be totally unsuitable for evaluation of the overall impact of coronary artery surgery or renal transplantation.

Quality-adjusted life year: Often a wide range of potential disabilities and death need to be considered. In an attempt to bring together these various factors including mortality, the QALY has recently been introduced.[6] QALY is an index designed to take account of both the quality and duration of survival in assessing the outcome of health-care procedures or services. It is derived from a modification of the standard life-table methods used to assess comparative outcome and the impact of various treatments in chronic conditions, in particular, malignant disease. The important difference with QALY is the incorporation of assessments of distress and disability based on the Rosser[7] classification of illness states (Table II). Evaluations for any particular disease situation are made from questionnaires completed by healthy normal persons, doctors and patients and include a measure of prognosis. The QALY scale ranges from 0 = death to +1 = a full and healthy life. Any grading >0.9 is considered to be a high-quality life.

The assumption implicit in the QALY method is that for each person in any specific situation of impaired quality of life, a reciprocal relation exists between duration and quality of survival. This is equivalent to posing the direct question to the subject, "To what extent would you accept a shortening of your present expectation of life as the price for a complete restoration of health and/or freedom from potential disability?"

There are a number of significant practical difficulties in setting up the QALY assessment for any particular situation.[8] These include the development of a set of quality adjustment fractions for the particular case, taking into account the many different ways life quality can be impaired, and ensuring that the required ratings are based on sample questionnaires from as wide a range of the general population as possible. Despite these difficulties QALYs have been successfully used to assess outcome in a variety of different situations. QALYs enable comparative assessments (including cost/benefit) to be made between widely different treatment methods for the same condition, and potentially between different disease processes.

TABLE II Rosser Classification of Illness States

Distress	
(A)	No distress
(B)	Mild
(C)	Moderate
(D)	Severe
Disability	
I	No disability
II	Slight social disability
III	Severe social disability or slight impairment of performance at work, or both
IV	Choice of work or performance at work severely limited
V	Unable to undertake any paid employment or continue any education. Old people confined to home unless accompanied
VI	Confined to chair or wheel chair or requiring help from assistant for normal mobility
VII	Confined to bed
VIII	Unconscious

PROBLEMS AND PITFALLS IN QUALITY OF LIFE ASSESSMENT

Scientific criteria: Questionnaires must be easily understood by patients from a range of educational and cultural backgrounds. Methods used to record responses must take these factors into account. In addition, questionnaires must be designed to cover the areas of interest and be able to detect both improvement and deterioration.[9] They may include visual analog scales, multiple-choice questions and measures of performance, including cognitive tests and activities of daily living scores (observer-rated assessments of self care).

Validity and reliability: Establishment of the validity of measures of QOL is difficult because there is no "gold standard" for comparison. In a trial, validity may be implied by a change in a similar direction for scores from different measures of QOL (e.g., symptom reduction and improvement in activity scores). Reliability of measures is assessed by the consistency of test and repeated test results, and the degree of variability between observers of the same subjects and on different occasions.[10] The QALY index has been shown to have a high degree of repeatability and reliability.

Patient selection: Patients entering trials are by definition a selected group because they must be fit enough to enter the trial and are likey to be compliant with their medication. An additional requirement for entry into QOL assessment trials is their ability to complete questionnaires or tests. These, as mentioned previously, must therefore be applicable to a wide range of patients. Place and time of questionnaire completion must be standardized to avoid bias. For example, questionnaires administered after the completion of an exercise test in a heart failure trial may strongly reflect the subjects' awareness of their degree of measured improvement or lack of it during the treadmill exercise.

"Blinding" and placebo control: Whenever possible patients and investigators must be blinded to the treatment protocol and a placebo control should be used. This is as important for QOL assessment as for any other scientific evaluation. Investigators are likely to have preconceptions about the benefits and potential adverse effects of treatments that will invalidate the assessments. This may also be an important factor in deciding whether the questionnaires should be self-administered by the subject or delivered in a question-and-answer session by the investigator. Randomization should also be used to minimize bias. However, this may not overcome the strong differential placebo effect on "well-being" between surgical and medical treatment, e.g., the powerful placebo effect demonstrated after sham internal mammary artery ligation operations for angina.[11]

Statistical analysis of results: Evaluation of treatment effects depends on analyses before and after the trial. The validity of this assessment depends on the inclusion of all subjects (i.e., withdrawals and deaths) in order to avoid major sources of bias. This is of particular importance when evaluating QOL in diseases with a high mortality and when comparing medical and surgical intervention in which operative mortality is obviously a significant adverse outcome. For example, the United Kingdom Cardiac Transplant Study showed a significant and probably not unexpected improvement in QOL in transplanted patients. This result, however, was based on the assessment of the 62 long-term survivors of the operation although 169 patients received transplants.[12] The inclusion in the QALY assessment of a measure of prognosis is an attempt to deal with this kind of problem.

CONCLUSIONS

There is increasing interest in the use of QOL assessment to evaluate the outcome of treatment of a number of disease processes. Evaluation of QOL is difficult and is influenced by a variety of patient factors. A perfect method of assessment is not available, although the use of QALYs has been particularly successful in comparative and cost-benefit analyses. Whichever method of assessment is used, the conduct of the investigation and adherence to high standards of scientific clinical trials procedure are mandatory to ensure confidence in the results.

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Workshop Discussion

Dr. Oakley (London, United Kingdom): Professor Williams, the economist who invented quality adjusted life years (QALYs), has used them to suggest that because hip replacement produces better results than coronary bypass surgery it should be performed in preference to coronary bypass surgery. I think that is an absolute travesty of the way that QALYs should be used to design health economics.

Dr. Davies (Birmingham, United Kingdom): The initial database upon which QALYs was devised took into account only 70 patients. Another problem with QALYs is that more points are scored if the prognosis is altered than if the degree of mobility is altered. Therefore, if comparing the outcome of an operation such as surgery for a strangulated hernia against coronary artery bypass grafting for single-vessel or 2-vessel disease (i.e., one which is obviously altering prognosis against one which is alleviating symptoms), the treatment that achieves more in terms of QALYs is the surgical procedure chosen for funding.

Dr. Barnett (Leicester, United Kingdom): I think that QALYs as a concept is an extremely good idea. My concern is that they may be used by government, certainly in the United Kingdom, to indicate the best option economically. I think that this is wrong.

Dr. Northcote (United Kingdom): What methods should we use as practicing clinicians for assessing the benefits of drugs or other types of intervention? Should we be observing anaerobic thresholds and measuring lactate concentrations, and is it really worthwhile conducting an exercise distance test as a matter of course?

Dr. Oakley: We do all the simple tests and then select the more difficult ones as appropriate to the patient or to our program. Obviously we talk to the patient and examine and weigh him as a first step. After one has performed the simpler tests, which include electrocardiogram, chest radiographs and echocardiography (which is too insensitive where the left ventricle is dilated), exercise testing is the most valuable criterion of change in the patient's condition, but it should be realized that the patient with chronic heart disease can be trained if he is well motivated and he will improve irrespective of any improvement in his heart. I think that exercise testing and measuring $\dot{V}O_2$max is probably the best means of assessing the benefit of any treatment.

Dr. Northcote: The clinician doesn't always have access to a Cybex machine to measure $\dot{V}O_2$max. What should he do in these circumstances.

Dr. Oakley: I think that important information can be gathered by talking to the patient and finding out what he does at home. Even better, you could spend a little time to walk with him.

Dr. Drexler (Freiburg, Federal Republic of Germany): I think the important question is whether or not we should perform exercise testing on these patients. It would be desirable to conduct exercise testing in every patient that we treat in the clinical setting. I also think that gas analysis during exercise studies would be helpful. However, as far as the clinical care of patients goes, it is probably not worthwhile because it is time-consuming, very expensive and not everybody has access to such a machine. Concerning clinical studies, I think there are a couple of possible ways of overcoming this problem; we are examining the possibility of taking serial lactate measurements during exercise and with these measurements determining the anaerobic threshold. Whether this measurement would help us detect very sensitive drug effects over a long period of time is also being considered. For the acute part of this study, for which we have enrolled more than 60 patients, there is excellent agreement between lactate measurements performed serially during exercise, and exercise capacity, anaerobic threshold and maximal oxygen consumption as measured with gas analysis, which is a much more tedious and expensive method. Whether this helps us to evaluate the benefits of long-term therapy is still unknown, because there are many problems in assessing whether lactate metabolism is changed by a drug. For example, an angiotensin-converting enzyme (ACE) inhibitor could change lactate metabolism in the liver, liver perfusion and lactate uptake. An ACE inhibitor could also change lactate uptake in nonexercising muscle, and this is not a real drug effect in terms of what would benefit the patient. So we still have to determine whether this would help us to assess the benefit of drug therapy. If lactate measurements during exercise prove to be a sensitive indicator, this would help us to perform a simple test for the potential benefit of long-term treatment.

Dr. Cohen Solal (Paris, France): If you consider the prognosis of the patient, one has to focus on the ventricular function. A patient with an ejection fraction of less than 10%, if he has a good exercise tolerance, I would think, has a poor prognosis, but if you deal with his daily life activities that is not the same as his prognosis, you have to deal with exercise tolerance. I think that measuring oxygen uptake is the best way of measuring exercise tolerance because it has a high reproducibility. Alternatively, a controlled walk test should be used. Improving oxygen uptake entails a delayed action, and if peak oxygen uptake is not improved in a patient it does not mean that the drug has had no effect. For example, diuretics dramatically improve the quality of life of patients, but they do not improve peak oxygen uptake without training, and I think the case is the same for nitrates. For this reason, a submaximal exercise test would be more appropriate for assessing the effect of a drug. If we are looking at a new drug entity and specifically want to prove that it is effective, then I think that all the tests discussed should be conducted. From the point of view of assessment in the clinic I would agree entirely with Dr. Oakley; it is a matter of talking to your patient and using certain clinical judgments.

Dr. Parmley (San Francisco, California): What sort of exercise protocol should we perform and what sort of exercise machine should we use?

Dr. Cohen Solal: Concerning the machine, I think that the treadmill mimics the daily life activity of our patients more closely. However, it is more difficult to measure oxygen consumption with a treadmill than on a bicycle. Most authors consider the ramp test protocol to be the best method available. Maximal exercise is achieved more easily following this protocol and less artifacts appear on the electrocardiogram. Concerning the submaximal exercise test, the idea was proposed some years ago, but until now I am unaware of anyone having found the perfect end point of this exercise.

Dr. Barnett: I tend to favor the corridor walk test. Patients, particularly elderly patients, cannot manage on treadmills very easily, because though it may mimic their activity, they are not accustomed to walking in this way. In our department, the patient walks the corridor at whatever rate they like for a period of 6 minutes. That I think is not an unreasonable compromise. I don't know what other people think but we tend to use it.

Dr. Parmley: I think the principle that many of you follow is to be with the patient during the time of exercise and observe them in order to determine how well they are performing. In the patient who has severe heart failure with a relatively limited life expectancy and who is not a candidate for transplant or any other dramatic form of therapy, which, in your view, would the patient like most—a prolongation of life or an improved quality of life, even if it were shortened? Should drugs be given to patients that we know may improve short-term exercise tolerance, but actually have been shown to shorten life?

Dr. Barnett: That is an impossible question to answer, the reason being that you have not defined your parameters. You have not defined them on the basis of age, sex of patient, ethnic group or country of origin. I believe that what may be applicable to one group of patients, may not be applicable to another. An 87-year-old may simply want to be able to walk to the shops or be able to walk upstairs rather than have an increased lifespan. However, a 35-year-old with a viral myocarditis would be more likely to want a heart transplant rather than drug therapy.

Dr. Parmley: The Food and Drug Administration gets very upset by the notion that we might give drugs that shorten but improve quality of life, and that is partly the reason I am asking the question.

Dr. Cohen Solal: I agree entirely with Dr. Barnett, and it is a problem for us, for example, for longer studies with enoximone and milrinone patients have improved quality of life during the first weeks or months, but we cannot prolong therapy with this drug.

Dr. Oakley: The drug should perhaps be used just in the run-up to transplantation, but of course there is no run-up for most people, because only a small proportion of the patients referred for transplants in England will ever be transplanted.

Speaker: What is the place for training and reeducation of patients with severe heart failure? You have illustrated that training improves quality of life and exercise tolerance, but doesn't exercise training have detrimental effects on lung or cardiac hemodynamics or renal function?

Dr. Drexler: This was the study from Sullivan and coworkers.[1,2] They selected the patients for this training program very carefully, but I don't want to imply that you should take all patients with severe heart failure and train them. Some of them will not do it, and in others it might be dangerous. In the clinical setting, patients tend to be detrained by several doctors telling them not to do anything strenuous, and in the long run this does not help them. On the other hand, if you are able to keep those patients at a certain level of physical activity, it may promote structural vascular changes in the periphery; combined with therapy, the vessels may be opened up resulting in afterload reduction which finally unloads the ventricle and improves neurohumoral regulation. So I think a controlled method of increasing physical activity helps the patient in the long-term run. However, physical activity should not be overdone and patients should be carefully selected.

Speaker: What do we actually want for the patient and what should we do for him? Why don't we just try to help the patient to accept what he actually can do? Another point of quality of life is to accept what you have and this has not been mentioned so far.

Dr. Oakley: I agree absolutely. A depressed patient with a normal heart has a very poor quality of life, if he is very depressed, and many patients with heart failure are and the quality of life is much lower than it would be if they were feeling more optimistic, irrespective of what they are able to do. Working on the patient's psyche could add tremendously to their quality of life. I think that the ACE inhibitors have done a great deal for the quality of life over and above what they have done for the performance of the heart, simply because patients using ACE inhibitors feel better. Some of them feel slightly euphoric and therefore their quality of life is improved out of all recognition.

Dr. Stiles (Durham, North Carolina): A patient presenting with a very large ventricle, a large heart and a bad ejection fraction indicating severe left ventricular dysfunction should be considered as an example. Many doctors would tell this patient not to overexert himself. However, on a treadmill or exercise test he had a normal oxygen consumption and peak oxygen consumption and was physically active. There is good evidence that these patients should do what they want in terms of physical activity, unless they actually contract symptoms. That is to say they should stop exercising strenuously before they go too far, and many patients know how far they can go. We have had a program at Duke University called DUPAC (Duke University Preventative Approach to Cardiology). It is for people who are at high risk of developing coronary disease as well as those who have coronary disease or congestive heart failure. This program is not conducted in a hospital; it is run at athletic facilities. It is a lifestyle management approach. Patients do not come to the program and participate in their normal clothes; they must wear sports clothes, so even in the people with severe congestive heart failure whose total "exercise" may be moving their arm several times an hour initially are made to feel that they are not sick in the hospital, but that they are learning to function in life. It is dramatic to see how people with ejection fractions of 8% improve over 6 months to 1 year. It makes them feel as if they are normal, helps their depression and eventually develops their muscles. As Dr. Drexler has mentioned, you do not improve left ventricular function over time, but you improve your peripheral adaptation to exercise and improve because your muscles are more efficient, and I think that this approach is a very effective one.

Dr. Oakley: What effect does the drop-out of the patients with an ejection fraction of 8% have on the other patients who still have not dropped out?

Dr. Stiles: That is something that is actually addressed in sessions as people enroll. They all realize that the group is diverse, some of the participants are 30-year-old people who are very fit but whose fathers and grandfathers died at the age of 40; others are 70-year-olds who have an ejection fraction of 10%. They all realize that it is a heterogeneous group, and that their goal is to help each other. People who have ejection fractions of 10% and are physically active work together with the less able participants to improve themselves as a support group; they see themselves as a support group providing positive feedback to each other. Occasionally, participants have infarcts during their training. This is unusual, but it happens and it is amazing to see the other participants show up in the hospital to give them their support.

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Acute and Chronic Hemodynamic Effects of Xamoterol in Mild to Moderate Congestive Heart Failure

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IMPORTANT: See 'Addendum', page 54C.

Xamoterol, a new β_1 partial agonist, has the potential to modulate cardiac response to variations in sympathetic tone in patients with heart failure. Its properties should result in β-receptor stimulatory effects at low levels of sympathetic tone and β-receptor protective effects at higher levels of sympathetic tone. The acute effects of intravenous (i.v.) xamoterol on hemodynamics at rest and during exercise were studied in 30 patients with mild to moderate heart failure (13 patients in New York Heart Association class II; 17 in class III) due to ischemic (n = 24) or cardiomyopathic (n = 6) heart disease. Cardiac index, stroke volume and stroke work index at rest were significantly improved after i.v. administration of xamoterol and consistent with net agonist effects. During exercise, heart rate and double product were significantly reduced (net antagonist effects), but with preservation of the expected increases in cardiac index and systolic blood pressure. These hemodynamic findings confirm the ability of xamoterol to modulate cardiac response to variations in sympathetic tone. Tachyphylaxis and arrhythmogenicity limit the chronic use of drugs with full β-agonist properties as positive inotropes in heart failure. The patients were therefore entered into a 6-month double-blind, placebo-controlled, crossover study of chronic oral xamoterol therapy, 200 mg twice daily, and the hemodynamic responses to i.v. xamoterol were repeated at the end of the trial. No impairment in either resting or exercise effects was observed, indicative of a maintained response and absence of tachyphylaxis after chronic therapy. Furthermore, 24-hour ambulatory electrocardiographic monitoring showed no change in ventricular arrhythmias during oral treatment. In mild to moderate heart failure, xamoterol improves cardiac performance at rest and during exercise, the changes being consistent with its pharmacologic profile. There was no evidence of tachyphylaxis or exacerbation of ventricular arrhythmias after chronic oral therapy.

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The sympathetic nervous system is activated early in heart failure as a normal compensatory mechanism, with norepinephrine providing natural endogenous inotropic support to the failing heart.[1-5] The final common pathway regulating contraction (β-receptor/adenylcyclase/cyclic adenosine monophosphate system) needs to remain intact to enable the heart to maintain the same level of response to circulating catecholamines. However, it is now well recognized that chronic sympathetic nervous system overactivity seen in heart failure has deleterious effects on this pathway leading to β-receptor down-regulation.[6-14] This loss of β-receptor function or number subsequently deprives the heart of its ability to respond to inotropic support explaining the clinical findings that plasma norepinephrine concentration correlates with prognosis[5,15] and that progressive heart failure occurs despite therapy with therapeutic regimens that do not influence, or that increase, sympathetic drive. Furthermore, enhanced β-receptor down-regulation resulting from exogenous inotrope therapy would explain the frequent occurrence of tachyphylaxis to such agents,[12] and would also explain why no inotrope improves, and why some worsen, prognosis.[16-18] Conversely, angiotensin-converting enzyme inhibitors have been shown to improve prognosis;[19] this may be due, at least in part, to their ability to provide vasodilatation associated with reduced, rather than increased, sympathetic drive with a consequent restoration of β-receptor function.[20] Similarly, the apparent paradoxic use of β antagonists in severe heart failure aimed at protecting β-receptor function has been shown to have beneficial effects in selected groups of patients.[21-23] However, removal of sympathetic support when pure β antagonists are being administered to patients with heart failure is potentially hazardous.

Xamoterol is a cardioselective β_1 partial agonist with 43% of the intrinsic sympathomimetic activity of the full agonist isoprenaline.[24] This novel profile provides the potential to modulate the cardiac responses to variations in sympathetic tone. At relatively low levels of sympathetic tone, such as at rest in mild to moderate heart failure, occupancy of the β receptor by xamoterol should result in a net agonist effect. However, at higher levels of sympathetic tone, occurring during exercise, a net antagonist effect should predominate because of competitive inhibition of norepinephrine at the receptor level. This study reports the hemodynamic effects of xamoterol in patients with mild to moderate heart failure at rest and during exercise, and was designed to determine whether this profile of net agonism/antagonism, dependent on the

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background level of sympathetic tone, occurs. The effects of xamoterol on ventricular arrhythmias and its potential to prevent the development of tachyphylaxis resultant on the stabilization of β-receptor stimulation is also examined.

METHODS

Patients: The study group consisted of 30 patients (27 men, 3 women, mean age 60 ± 2 years, range 40 to 73 years) with mild to moderate heart failure (New York Heart Association class II [n = 13]; class III [n = 17]) due to ischemic (24 patients) or cardiomyopathic (6 patients) heart disease. During the study, concomitant therapy with xamoterol consisted of digoxin (12 patients), vasodilators (nitrates, calcium channel antagonists or ACE inhibitors, 16 patients) and diuretics (frusemide and/or amiloride, 28 patients).

All patients underwent a symptom-limited exercise test on a bicycle ergometer 1 to 2 weeks before their initial hemodynamic study to determine their exercise capacity. The initial work load of 25 watts was maintained for 3 minutes and then increased by 25 watts every 3 minutes. The patients were selected on their ability to complete a minimum of 3 minutes of this exercise protocol with dyspnea as their limiting symptom.

STUDY PROTOCOL

Initial invasive hemodynamic assessment: A thermodilution Swan-Ganz catheter was inserted through the right subclavian vein and an intraarterial cannula was sited percutaneously into the right brachial artery. All hemodynamic measurements were obtained with the patient in a semirecumbent position at 25° from the vertical. Hemodynamic variables at rest were recorded 1 hour after catheter insertion. The patient then performed a symptom-limited bicycle exercise test, with hemodynamic variables recorded during the last 30 seconds of each stage. Left ventricular ejection fraction was measured by radionuclide technetium-99m scanning at rest and during the last 2 minutes of each 3-minute exercise stage. Thermodilution cardiac output was determined in triplicate. The patients were then allowed to rest for 4 hours and at the end of this period hemodynamic measurements at rest were recorded again, before and 15 minutes after intravenous (i.v.) administration of xamoterol, 0.2 mg/kg. The exercise test was then repeated as mentioned before.

Chronic oral dosing: After these initial hemodynamic assessments the patients were entered into a 6-month, placebo-controlled, double-blind, crossover study of oral xamoterol, 200 mg twice daily.

Final hemodynamic assessment: At the end of the chronic oral dosing phase, and after a 72-hour washout period, the hemodynamic assessments at rest and during exercise before and after i.v. administration of xamoterol, 0.2 mg/kg, were repeated in the same manner as mentioned.

Twenty-four-hour ambulatory electrocardiography: Ambulatory electrocardiographic monitoring (Oxford Medilog 4000 II) was performed in all patients before the initial hemodynamic assessment and repeated in the last week of each treatment phase during oral therapy. Mean hourly heart rates over the 24-hour period were obtained directly from computer analysis (Oxford Medilog 4500). The mean hourly ventricular ectopic frequency and arrhythmia classification were analyzed by direct visual analysis of each 24-hour disclosure.

Statistical analysis: The significance of differences was analyzed using Student's *t* test for paired observations. Values are expressed as mean ± standard error of the mean; $p < 0.05$ was considered significant.

RESULTS

Initial hemodynamic assessment: In patients at rest, i.v. xamoterol induced a small but significant decrease in heart rate (78 ± 3 to 74 ± 2 beats/min, $p < 0.05$) associated with significant improvements in cardiac index (2.51 ± 0.15 to 2.80 ± 0.14 liters/min/m^2, $p < 0.001$), stroke volume (62 ± 4 to 75 ± 5 ml/beat, $p < 0.001$) and stroke work index (42.4 ± 3.6 to 47.7 ± 3.9 g·m/beat/m^2, $p < 0.01$). Systolic blood pressure was maintained (148 ± 4 to 142 ± 4 mm Hg) with a small but significant decrease in diastolic blood pressure (87 ± 2 to 81 ± 2 mm Hg, $p < 0.01$) and systemic vascular resistance (1,990 ± 141 to 1,699 ± 112 dynes/s/cm^5, $p < 0.01$). There were no significant changes in either pulmonary artery wedge pressure (13.7 ± 1.5 to 13.5 ± 1.5 mm Hg) or ejection fraction (35.2 ± 2.9 to 35.0 ± 3.0%). Double product at rest was significantly reduced (1,146 ± 46 to 1,051 ± 41 mm Hg/min × 10^{-1}; $p < 0.05$).

During exercise, the most significant observation after i.v. xamoterol administration was a reduction in exercise heart rate (112 ± 4 to 97 ± 3 beats/min, $p < 0.001$). Despite this attenuation in heart rate the expected increases in cardiac index and systolic blood pressure during exercise were maintained (4.61 ± 0.27 to 4.70 ± 0.27 liters/min/m^2 and 166 ± 6 to 164 ± 5 mm Hg, respectively). This preservation in cardiac index at lower heart rates was due to maintenance during exercise of the significant improvements in stroke volume observed at rest (81 ± 6 to 95 ± 7 ml/beat, $p < 0.001$). Similarly left ventricular stroke work index was significantly improved on exercise after i.v. administration of xamoterol (56.6 ± 5.6 to 62.3 ± 5.3 g·m/beat/m^2, $p < 0.05$). Because of the effects on heart rate, exercise double product was significantly reduced (1,864 ± 92 to 1,599 ± 76 mm Hg/min × 10^{-1}; $p < 0.01$). Exercise time increased by 10% (424 ± 21 to 463 ± 25 seconds), although this just failed to reach significance ($p = 0.06$). There was no significant change in exercise ejection fraction (37.0 ± 4.0 to 39.2 ± 4.5%).

Chronic oral dosing: Four patients were withdrawn from the study during the chronic oral phase. In 3 patients this was due to progressive heart failure during the first phase of the study. All 3 patients were receiving placebo in addition to their normal therapy. The fourth patient was withdrawn from the trial because of headaches occurring after placebo during the second phase of the protocol.

Final hemodynamic assessment: For technical reasons full resting and exercise hemodynamics were only available in 23 of the 26 patients who completed the chronic oral dosing phase of the study. The hemodynamic indexes at rest, before rechallenge with i.v. xamoterol

TABLE I Ventricular Arrhythmias During Chronic Oral Xamoterol Therapy (200 mg twice daily)

	Baseline	Placebo	Xamoterol
Mean hourly ventricular ectopics (beats/hour)	56 ± 42	18 ± 7	30 ± 17
Complex forms (no. of pts.)	19 of 26	19 of 26	20 of 26
Ventricular tachycardia (no. of pts.)	4 of 26	6 of 26	5 of 26

were similar to those at the initial assessment. After chronic oral xamoterol therapy, i.v. xamoterol, 0.2 mg/kg, again resulted in a small, but on this occasion nonsignificant, decrease in heart rate at rest (78 ± 4 to 75 ± 3 beats/min). Cardiac index at rest was again significantly improved (2.6 ± 0.2 to 2.8 ± 0.2 liters/min/m^2, $p < 0.05$) as a result of significant improvements in stroke volume (67.1 ± 4.9 to 74.6 ± 5.6 ml/beat, $p < 0.01$). The effects of i.v. rechallenging with xamoterol on exercise hemodynamics were also the same as before chronic oral xamoterol therapy. There was a marked attenuation in exercise heart rate (110 ± 5 to 96 ± 4 beats/min, $p < 0.001$) with preservation of the expected increases in cardiac index (5.1 ± 0.3 to 5.0 ± 0.3 liters/min/m^2) and systolic blood pressure (183 ± 7 to 178 ± 8 mm Hg, difference not significant) due to significant improvements in exercise stroke volume (91.3 ± 6.5 to 104.4 ± 8.6 ml/beat, $p < 0.01$).

Twenty-four-hour ambulatory electrocardiography: A complete series of 24-hour ambulatory recordings was obtained in all 26 patients. All but 1 patient had ventricular ectopic activity. The mean hourly ventricular ectopic frequency before xamoterol therapy was 56 ± 42 ventricular ectopic beats/hour. Nineteen patients had complex forms (multiform ventricular ectopies, pairs, nonsustained ventricular tachycardia). During chronic oral xamoterol therapy, there was no significant change in the mean hourly ventricular ectopic frequency or the presence of complex ventricular arrhythmias (Table I).

Oral xamoterol therapy resulted in a stabilization of the variations in heart rate during each 24-hour period. During the daytime and periods of activity, the mean hourly heart rates were reduced, whereas at rest during the night the mean hourly heart rates were increased (Fig. 1).

DISCUSSION

Intravenous xamoterol results in significant improvements in cardiac index, stroke volume and left ventricular stroke work index at rest, which are consistent with a net agonist effect when sympathetic tone is relatively low. Similar results have been reported in other smaller studies assessing some of the hemodynamic parameters recorded here.[25-34] In this study, hemodynamic improvements were associated with a small but significant decrease in heart rate at rest. In other studies, small increases in heart rate have been observed and overall the absolute change in heart rate will be determined by the

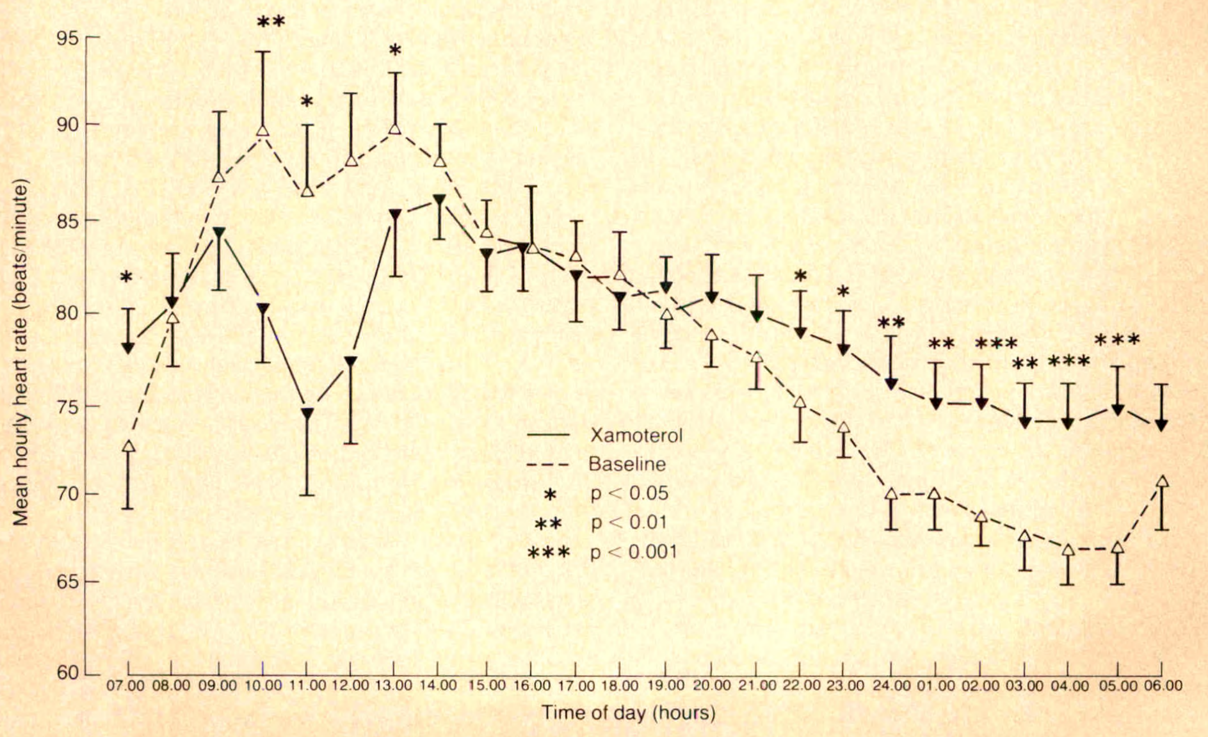

FIGURE 1. The effect of oral xamoterol, 200 mg twice daily, on the mean hourly heart rate over 24 hours using ambulatory electrocardiographic monitoring.

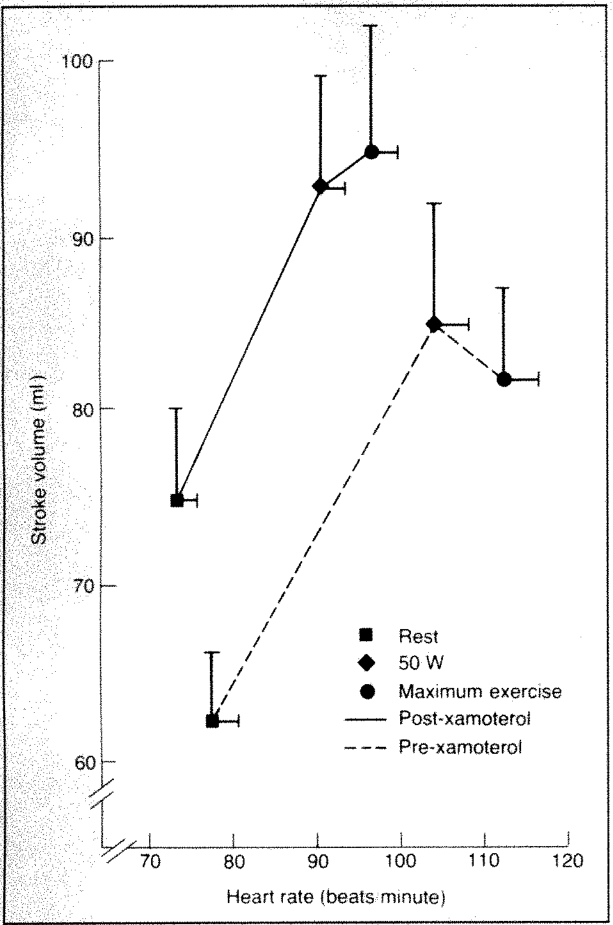

FIGURE 2. Relation between heart rate and stroke volume at rest and during exercise, before and after intravenous xamoterol, 0.2 mg/kg. Values are mean ± standard error of the mean.

level of background sympathetic tone in individual patients.

The marked attenuation in heart rate during exercise after xamoterol treatment is consistent with a net antagonist effect when sympathetic tone is raised. However, this was not at the expense of other hemodynamic parameters; expected cardiac output and systolic blood pressure increases during exercise were maintained due to continued improvements in stroke volume. These observations concur with the few other studies reporting the effects of xamoterol on exercise hemodynamics, when the most significant effects seen are attenuations in exercise heart rate.[25,28,29,34] If the hemodynamic changes at rest and during the different stages of the exercise protocol are analyzed, then for any given heart rate, stroke volume is improved (Fig. 2) and for any given filling pressure, left ventricular stroke work index is increased (Fig. 3).

The hemodynamic profile reported in this study is consistent with the dual effect of xamoterol, which is dependent on the background level of sympathetic tone and its ability to modulate cardiac responses to variations in sympathetic activity. The effects on mean hourly heart rate confirm this dual effect, with an overall reduction in heart rate during the daytime when the patient is active and sympathetic tone is increased. The mean hourly heart rate when at rest during sleep is increased when sympathetic nervous system activity is reduced (Fig. 1).

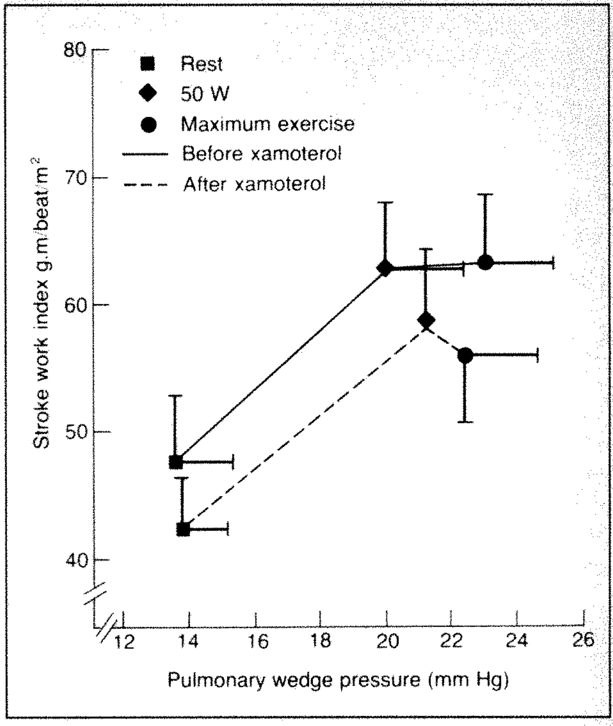

FIGURE 3. Relation between stroke work index and pulmonary capillary wedge pressure, at rest and during exercise, before and after intravenous xamoterol, 0.2 mg/kg. Values are mean ± standard error of the mean.

The significant reductions in double product both at rest and during exercise are important associations with the improved hemodynamics after i.v. administration of xamoterol, since in many cases heart failure is due to ischemic heart disease.

Unlike many other drugs with positive inotropic properties used in the treatment of heart failure, xamoterol showed no evidence of tachyphylaxis in either the agonist effects at rest or the antagonist effects during exercise after chronic therapy. Similar cardiac function was observed before and after i.v. dosing at the final assessment compared with the initial assessment. This lack of tachyphylaxis may be related to the potential to preserve β-receptor function[35] due to stabilization or to modulation of the degree of receptor stimulation, with xamoterol providing "agonist-support" and "antagonist-protection" depending on the level of sympathetic drive to the failing heart.

In patients with heart failure, approximately 50% of deaths are sudden and presumed to be arrhythmogenic in origin.[36] Many therapeutic agents, but particularly those with inotropic properties, have the propensity to increase ventricular arrhythmias, thereby seriously limiting their usefulness and potentially increasing mortality.[16,37] This patient group monitored by 24-hour ambulatory electrocardiography demonstrated the common finding of frequent ventricular ectopic activity in association with heart failure. Despite the beneficial hemodynamic effects and inotropic properties of xamoterol, this was not at the expense of an increase in ventricular arrhythmias.

CONCLUSION

Xamoterol improves cardiac function at rest and during exercise in patients with mild to moderate heart failure. These hemodynamic and ambulatory electrocardiographic data support the pharmacologic profile of net agonist/antagonist effects depending on the underlying level of sympathetic tone. Chronic oral therapy was not associated with significant adverse effects or any increase in ventricular arrhythmias, and there was no evidence of tachyphylaxis associated with either the agonist or antagonist effects. The ability to modulate cardiac responses to variations in sympathetic tone occurring at rest and exercise in patients with heart failure may be beneficial in preserving β-receptor function and thus maintaining therapeutic responsiveness.

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DISCUSSION

Dr. McInnes (United Kingdom): You showed uncontrolled data illustrating the effect of xamoterol before and after administration. Why did you choose to study these important responses in this uncontrolled manner? You then conducted a well-controlled study, but did not actually show us any results. Why was that?

Dr. Davies (Birmingham, United Kingdom): By uncontrolled I presume you mean that the acute intravenous dosing was not performed in a double-blind fashion. The reason was that these patients had been instrumented with Swan-Ganz catheters and intraarterial lines. Their responses to a similar volume of injectate was already determined in relation to their hemodynamic studies.

Dr. McInnes: I was not concerned about the study not being double-blind. I do not think that with objective end points this matters greatly, but the sequence effect is something you have to bear in mind, and more patients were given treatment than were not given treatment.

Dr. Davies: Although I have not presented all the tachyphylaxis data, I have actually analyzed it in exactly the same manner as you are suggesting, depending on whether patients received placebo last or xamoterol last, and there was no effect of sequencing.

Dr. McInnes: I take it then that there was a beneficial effect of xamoterol in the long-term study.

Dr. Davies: Indeed. I have shown you the group data; I could show you virtually the same data with the same statistics if you compared those who received xamoterol last to those in the initial hemodynamic exercise test.

Dr. Drexler (Frieburg, Federal Republic of Germany): What was the wedge pressure during exercise after long-term treatment? The reason why I ask this is because, in your studies, the cardiac output during exercise did not change after long-term treatment, and, at least in the acute study, wedge pressure during exercise did not change. What is the reason for this finding and why do you think exercise tolerance is improved?

Dr. Davies: One of the reasons that exercise tolerance improves is because the heart rate is reduced; hence, the double product is decreased and the degree of myocardial oxygen demand reduced. On the basis of the etiology of heart failure in this group of patients being ischemic heart disease, I think that is probably a major reason why they were able to exercise for longer; they are actually exercising at much lower heart rates. Xamoterol also affects cardiac filling which was not assessed during this study. Although other researchers have demonstrated a long-term adaptation in the wedge pressure response to exercise, we did not.

Dr. Camerini (Italy): Were there any important side effects after intravenous injection of xamoterol?

Dr. Davies: One of the 30 patients in the trial experienced an increase in dyspnea 48 hours after his first hemodynamic exercise test. He then responded to an intravenous dose of diuretic after which there were no further problems. Whether the increased dyspnea was related to intravenous xamoterol treatment is difficult to establish because it occurred 48 hours after receiving an intravenous dose of the drug. I have studied hemodynamic responses after oral dosing with xamoterol, 200 mg, in a group of 12 patients with severe heart failure (i.e., severe heart failure despite the concurrent therapy that they were receiving). Only 1 patient suffered any adverse effect and, interestingly, his hemodynamics were different from other patients because he had a marked resting tachycardia, and may well have been running on a chronotropically driven heart with very little inotropic reserve. So, in answer to your question directly, no, there were no problems with the intravenous dosing. However, as you know, xamoterol is contraindicated in patients with more severe grades of heart failure since such patients may be critically dependent on all their cardio-sympathetic tone.

Speaker: Do you know if there is a relationship between the clinical response to xamoterol and the concentration of catecholamines in the blood?

Dr. Davies: Whether there is a net negative or a net positive chronotropic effect is reported by Sato et al. In this study the effect of xamoterol changes from net agonism to net antagonism at a norepinephrine concentration of between 400 and 500 pg/ml. In our study population, the mean norepinephrine concentration was approximately 450 pg/ml. Therefore, the dominant effect of xamoterol depends on the plasma concentration of norepinephrine in individual patients. The heart rate response observed was dependent on the degree of severity of heart failure and the degree of activation of the sympathetic nervous system. The important thing in successfully treating patients with this novel approach is that the heart is not left without a degree of agonist support (i.e. there is always a background level of agonist activity). Treatment in this way provides agonist activity when sympathetic tone is relatively low; this also prevents the deleterious effects of excessive sympathetic drive with activity.

Dr. Oakley (London, United Kingdom): You mentioned that the patient who was running on a chronotropically driven heart was perhaps least likely to benefit from xamoterol. In fact, these are the very patients who benefited most from the use of straightforward β blockers in trials conducted in Sweden before they extended the trials and saw a benefit in some patients whose resting heart rates were normal. How do you explain this?

Dr. Davies: What I really wanted to indicate was that this patient received a standard dose of the drug.

Dr. Oakley: I don't understand that either. It seems odd to be able to administer xamoterol, 200 mg twice a day, rather than to titrate it as one would with metoprolol.

Dr. Davies: That is exactly the point I am making. The patient received a standard dose in terms of the normal dose that produces these beneficial effects. If this sort of drug is used in a patient with a chronotropically driven heart, where the β-antagonist activity of xamoterol would predominate, then it should perhaps be administered at much lower doses initially in a similar manner to the Swedish β-blocker studies.[1] Our experience in severe heart failure and hemodynamics is very limited at present, and the important point is to think about the patient who may not do well on a standard dose in severe heart failure. We all obviously know that the compound is only currently marketed for mild heart failure and is contraindicated in the severest forms.

Dr. Kupper (Hamburg, Federal Republic of Germany): During the chronic oral treatment periods in your study, there were 4 withdrawals with placebo during the first 3 months and no withdrawals during the second placebo period. Would you suggest any training effect, such as occurs with dobutamine therapy for xamoterol?

Dr. Davies: Whether the patients effectively benefited in the second 3 months while on placebo because of the events occurring during the first 3 months while on xamoterol, I don't know. Certainly no patients had hemodynamic problems during the second phase while on placebo, though 1 patient withdrew due to headache. The 3 withdrawals due to progressive heart failure all occurred in the first phase during which time all patients were receiving placebo in addition to their normal medication.

Speaker: As most of your patients were coronary patients, did you analyze the ST changes during the test with and without xamoterol?

Dr. Davies: No, we did not. There is a study showing that in patients with ischemic heart disease and treated with xamoterol, a pronounced improvement in ST-segment change and time to ST-segment change occurs, but we did not study that in this group of patients.

Dr. Hori (Japan): Regarding the issue that xamoterol enhanced the inotropic effect during resting conditions, do you think it is necessary to enhance inotropism during the resting state? I think that in terms of exercise tolerance sympathetic drive is only necessary during exercise, and that xamoterol depressed the inotropic effect as well as the chronotropic effect. So, in terms of exercise tolerance the effect of xamoterol is inverted. Do you agree?

Dr. Davies: It is important to improve the patient's hemodynamics if possible at rest, and achieve an improved cardiac output and a decrease in systemic vascular resistance. Peripheral vasculature is perhaps the most important factor in patients with heart failure and that though central hemodymamics are also a problem, they may not be as important. With xamoterol treatment, the patient's resting systemic vascular resistance and resting cardiac output is improved. As illustrated in my presentation, the fall in systemic vascular resistance may be secondary to the improved cardiac output. You may find, therefore, that tissue perfusion may have improved. In patients with class II and III heart failure, I feel that it is important that their resting hemodynamics are as good as possible, and to improve on this when they exercise. One of the problems with exercise is, of course, that excessive sympathetic drive upsets stroke volume because the patient's heart rate increases. They then get further myocardial oxygen demand with all that follows, particularly if they have ischemic heart disease.

Dr. Hori: Which is greater: the antagonistic or the agonistic effect of xamoterol? Which is more important, do you think, particularly for the patient with cardiac failure?

Dr. Davies: Both effects are important. In terms of the overall possibilities on receptors and receptor function, one of the more important aspects would be to provide the patient with continuing inotropic support, but not by purely adding to the excessive receptor stimulation throughout the range of sympathetic drive. Hopefully in future observations, an effect on β-receptor function will be seen.

REFERENCE

1. Swedberg K, Hjalmarson Å, Waagstein F, Wallentin I. Beneficial effects of long-term beta blockade in congestive cardiomyopathy. *Br Med J 1980;44:117–173.*

ADDENDUM: Subsequent to this manuscript being written, changes were made to the prescribing information for xamoterol, restricting its use to patients with mild heart failure only.